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Original Communications

THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS*

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THE death rate from carcinoma of the female genital tract is approximately 32,000 per year in the United States and of this figure, four-fifths, or 26,000 deaths per year, may be said to be due to cancer of the uterus. This rate has remained practically constant during the past twenty-five years.[1]

One of the factors probably responsible for this rather discouraging situation is the fact that, despite the progress in methods of treatment, no significant improvement has been achieved in the diagnosis of malignant growths of the female genital tract, more particularly in their early stages. Indeed, it seems very likely that until enough is known about the etiology of cancer to make it possible to place efficient prophylactic weapons in physicians' hands, no radical change in the picture can be expected unless the introduction of new methods makes possible an early diagnosis of the disease.

Early diagnosis and treatment yield a high percentage of cures in both carcinoma of the fundus and of the cervix. The present difficulty in accomplishing an early diagnosis lies in the fact that we must depend largely upon the subjective symptoms of the disease to bring the patient to the physician, and by the time the patient becomes sufficiently aware

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of discomforts to seek help, the disease is far advanced. Even when the patient is seen early, the technique for making a positive diagnosis is not simple, as it involves a biopsy followed by the procedures necessary for microscopic examination, all of which are time consuming and relatively expensive. If by any chance a simple, inexpensive method of diagnosis could be evolved which could be applied to large numbers of women in the cancer-bearing period of life, we would be in a position to discover the disease in its incipiency much more frequently than is now possible. It is our purpose to present in this preliminary report the results of experimentation with such a method of diagnosis which appears to have great possibilities and which has been in use at the New York Hospital for the past eighteen months.

One of us (Papanicolaou) has studied the normal and abnormal variations in the vaginal smear in women and in animals for many years. Through these studies,[2, 3] which have been conducted since 1923 at the Woman's Hospital, at the New York Hospital, and at the Memorial Hospital, he has become aware of the fact that carcinoma of the fundus and carcinoma of the cervix are to some extent exfoliative lesions, in the sense that cells at the free surface of the growth tend to be dislodged and subsequently find their way into the vagina. Furthermore, a technique for collecting the cellular debris, smearing it upon glass slides, and staining it has been perfected, so that the various components may be studied. The method is so simple and inexpensive that it may be applied to large numbers of women.

METHOD OF TAKING THE VAGINAL SMEAR

A slightly curved glass pipette, 6 inches in length, 0.5 cm. in diameter, with a rounded tip and a small opening, and equipped with a strong rubber bulb for producing suction is used (Fig. 1)., The patient is placed upon an examining table in the lithotomy position. The labia are separated and the rubber bulb compressed. The glass pipette is introduced into the posterior fornix of the vagina. The pressure on the bulb is then released and the suction produced serves to aspirate vaginal fluid with its cellular content into the glass tube. While aspiration is in progress, the tip of the tube is moved from one side of the fornix to the other so that all parts are sampled. The pipette is then withdrawn, and the vaginal material is spread upon the surface of a clean microscope slide with a sudden pressure on the bulb. Further spreading with the convex side of the pipette is advisable when the amount of fluid is abundant, as in cases where there is considerable bleeding. Very thick smears are not well penetrated by the fixing fluids and cannot be uniformly stained.

The slides are immediately plunged into a solution of equal parts of 95 per cent alcohol and ether. Drying of the smears should be carefully avoided as it results in the loss of the sharp outlines of the cells and in a change in their staining reactions. The fixation does not require more than a few minutes, but smears may be kept in the alcohol-ether solution over a long period of time and may be shipped in bottles. It is recommended that the slides not be kept in the fixative for more than a week or two as the cells slowly tend to lose their normal staining reaction. If ether is not available, plain alcohol (95 per cent) can be used. For shipping slides, a square bottle 1¾ by 1¾ by 4½ inches may be used (Fig. 1). Such a bottle may hold as many as 7 or 8 slides. An ordinary paper clip attached to each or every other one of the slides (Fig. 1) prevents the smears from rubbing against one another.

A few precautions should be observed in the procurement of material for the vaginal smear. The vaginal contents should not have been disturbed by any form of examination or treatment. Douching or bathing will, of course, dilute or com-

pletely wash away the cellular deposits for a period of several hours. If there is a considerable amount of fluid of either serosal or sanguineous character, dilution will occur, in which case it is wise to make several smears to obtain the representative cell constituents which are ordinarily seen in a single smear.

METHOD OF STAINING VAGINAL SMEARS

Detailed instructions for staining vaginal smears are given by Papanicolaou in a recent article.[4] For general gynecologic diagnosis, stains DF20 or DF32 give satisfactory results. Slides are first stained in hematoxylin. A good nuclear staining is very essential for the recognition of malignant changes.

DESCRIPTION OF SMEARS SHOWING SQUAMOUS CARCINOMA OF THE CERVIX

Cervical malignancy, in our experience, is revealed in vaginal smears by the appearance of characteristic cells. These are, we think, derived from the superficial layers of the tumor which undergo continual desquamation. These cells show great variety of form and size, much greater

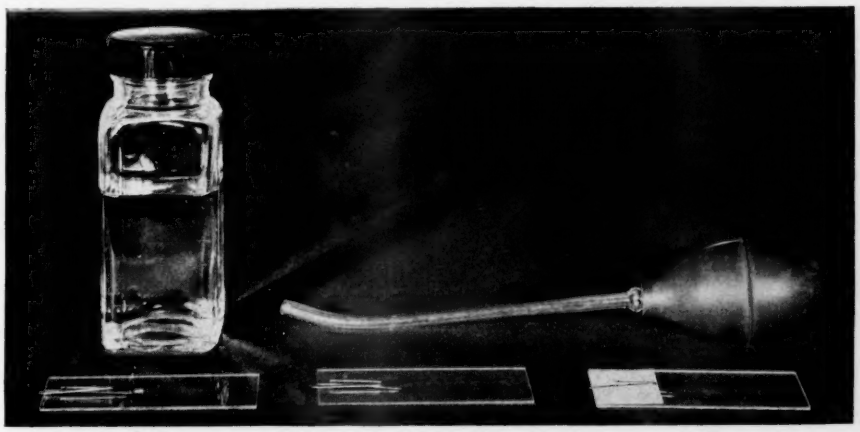

Fig. 1.—Pipette and bottle used for preparing vaginal smears.

than that seen in sections of the tumor. Their distinctive features lie in their structural abnormalities. They do not fall into the categories of any of the cell types found in the vaginal fluid of normal women or of women having benign tumors or other pathologic lesions of the uterus.

It is well to bear in mind that the isolated cells or at the most, groups of a few cells as seen in any smear preparation do not possess the orienting characteristics seen by the microscopist in tissue preparations of carcinomatous tissues, and that, therefore, a more intimate and critical knowledge of cytology is required for a correct interpretation. It is necessary, therefore, to enter into a detailed account of the characteristic appearance of the abnormal cells found in the vaginal smears of women harboring carcinoma of the fundus or cervix of the uterus.

The most characteristic feature of the abnormal cells is the atypical form and structure of their nuclei. These often are very large, far surpassing normal size (Figs. 3 and 4; compare with Fig. 2). The chromatin frequently shows a characteristic distribution in the form of conspicuous granules and of one or more small nucleoli (Figs. 3 and 4).

Some nuclei are in a stage resembling prophase as if they were undergoing changes preparatory to a mitotic division. Actual mitotic figures are very rarely seen. This is probably because of the fact that the epithelial cells found in the vaginal fluid are dead desquamated cells. The nuclei are often hyperchromatic and stain intensely (Figs. 2 and 3). Others

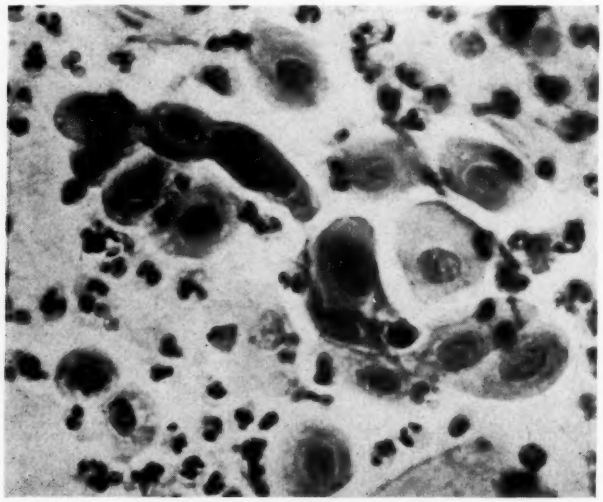

Fig. 2.—Group of normal basal cells. Menopause. ×800.

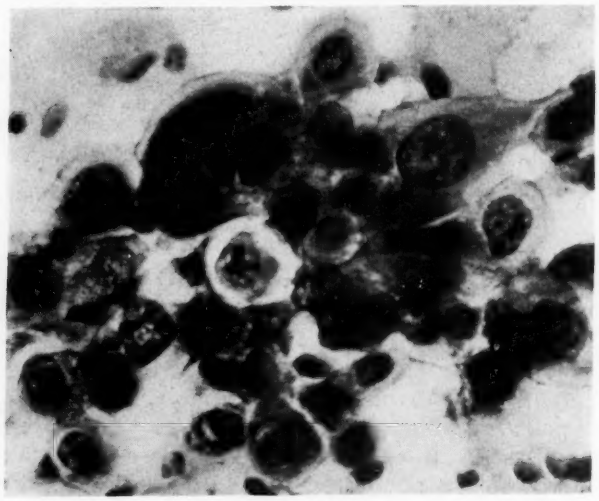

Fig. 3.—Group of abnormal cells. Carcinoma of cervix. ×800.

become very dense and lose their fine structure, whereupon they stain very deeply (Fig. 4). Small pyknotic nuclei as well as nuclei showing various degenerative changes are frequent. Some nuclei show indentations or irregular bulging. It is not unusual to find cells with more than one nucleus (Figs. 3, 4, and 5). This is probably the result of abnormal fragmentations or of amitotic divisions.

The cytoplasm also shows abnormal changes. It is often dense and hyperchromatic, particularly in the cells of the basal type (Figs. 3, 4, and 5). Such cells may appear either singly or in compact dark-staining clusters. Their form and size vary greatly. Some of the basal cells assume elongate, spindlelike, triangular, or amoeboid forms (Fig. 6).

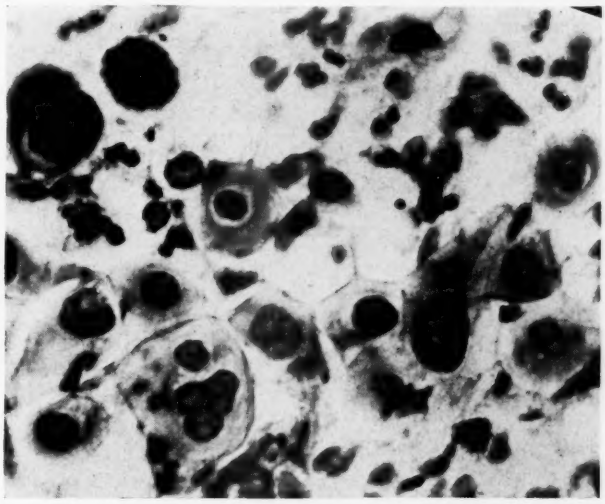

Fig. 4.—Abnormal cells. Carcinoma of cervix. ×800.

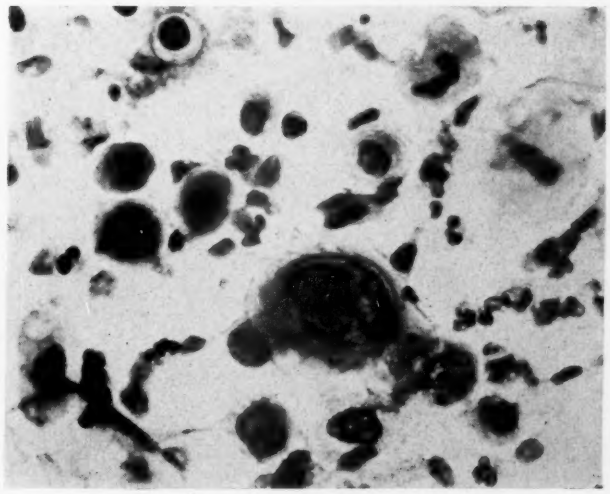

Fig. 5.—Abnormal cells. Carcinoma of cervix. ×800.

Basal cornified cells are not uncommon. Vacuolization of the cytoplasm is a characteristic feature (Fig. 7). The vacuoles may be empty or they may contain leucocytes, erythrocytes, cellular debris, or some pink-staining fluid. Sometimes the vacuoles occupy one side of the cell, while the dense cytoplasm and the nucleus are concentrated on the other side.

A commonly found, very characteristic cell type is an extremely elongated one resembling a smooth muscle fiber. Long fibrous cells of this type are modified epithelial cells and appear either isolated or in groups (Figs. 8 and 9). Another deformed cell type which is often seen is one having the form of a tadpole, with a spherical head containing

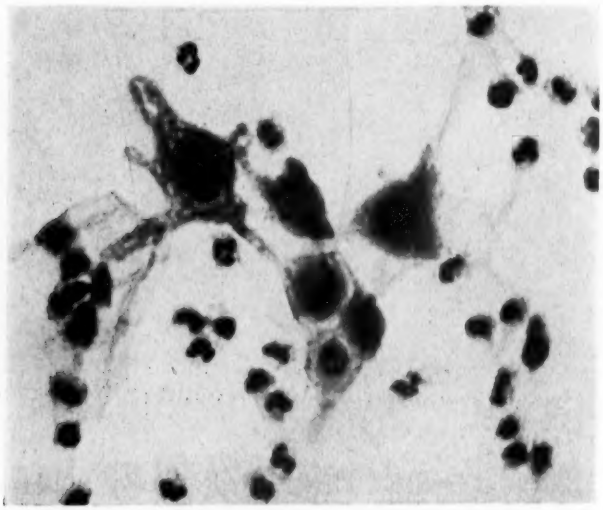

Fig. 6.—Group of aberrant basal cells. Carcinoma of cervix. ×800.

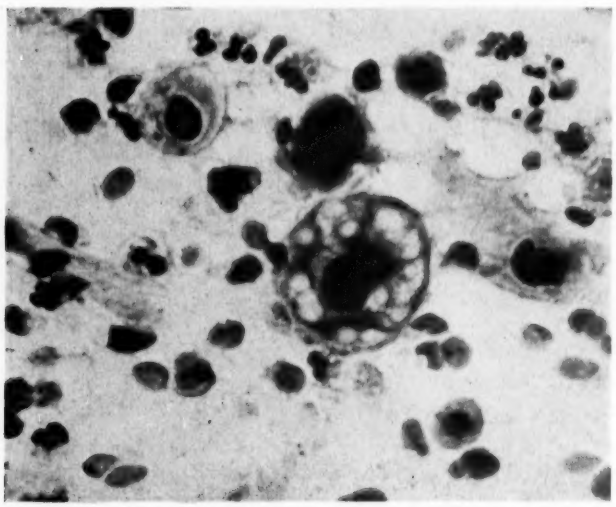

Fig. 7.—Abnormal vacuolated cell. Carcinoma of cervix. ×800.

the nucleus and a tail-like prolongation (Fig. 9). The bulging of the heavier part which contains the nucleus is sometimes placed more centrally, causing a narrowing of the cell at both ends. Other cells attain very large sizes and acquire the most unusual forms.

These "aberrant" cell types are numerous only in advanced cases of malignancy. They are relatively rare in the early stages of the disease and a thorough search of several slides is often necessary before their presence can be established. For this reason a negative diagnosis should always be made with extreme caution. Considering that even

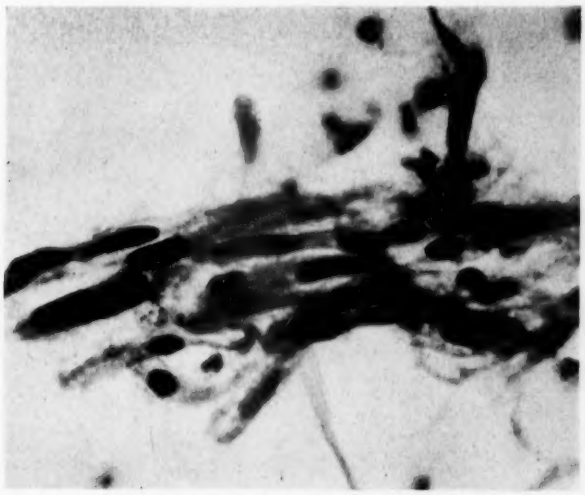

Fig. 8.—Abnormal epithelial cells showing extreme elongation ("pseudofibrous" type). Carcinoma of cervix. ×800.

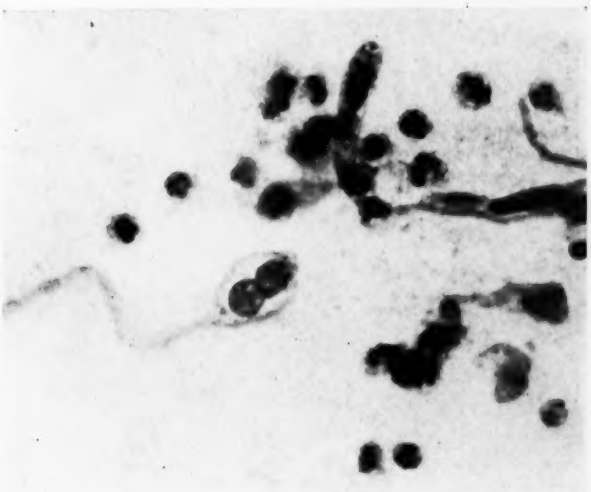

Fig. 9.—"Tadpole" cell with two nuclei, and other elongated cells. Carcinoma of cervix. ×800.

in the advanced cases the number of cells derived from the tumor forms only a small part of the total number of desquamated cells present within the vagina, it is natural to find the normal epithelial cells always in the majority. The large squamous superficial cells usually predominate in younger women, while the basal cells appear in larger num-

bers after the menopause. The relative number of these cells varies greatly. The number and the form of the cornified cells also show considerable variability. In some cases there is an excess of cornified cells, indicating a hyperestrin condition. This was observed more frequently

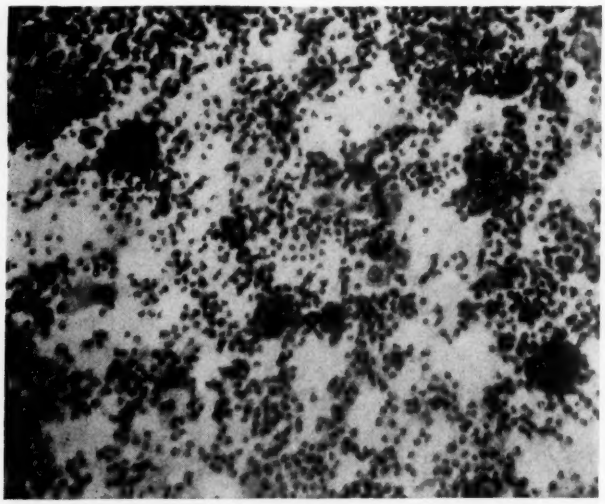

Fig. 10.—Extreme leucocytosis with clusters of polymorphonuclears. Carcinoma of cervix. ×220.

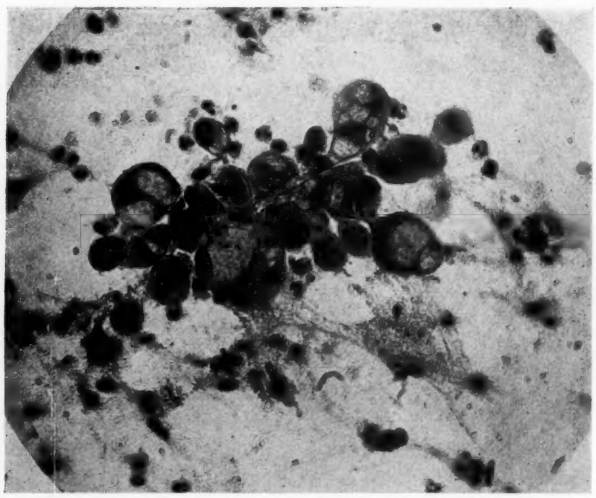

Fig. 11.—Group of abnormal histiocytes, some with very large vacuoles. Carcinoma of cervix.

in the early stages of malignancy. Cornification is sometimes due to the coexistence of other pathologic conditions like vaginitis or chronic cervicitis, or to the presence of trichomonas which is not uncommon in cases of cervical malignancy.

Blood elements are quite conspicuous in the vaginal smear of cervical malignancy. Erythrocytes are generally found in large numbers. Many

show degeneration and have lost their hemoglobin. Fibrination is very pronounced. The complete absence of blood is so rare even in the early stages that it may be considered in favor of a negative diagnosis. The leucocytes are as a rule very numerous, more particularly in the advanced cases (Fig. 10). The polymorphonuclears are often seen in

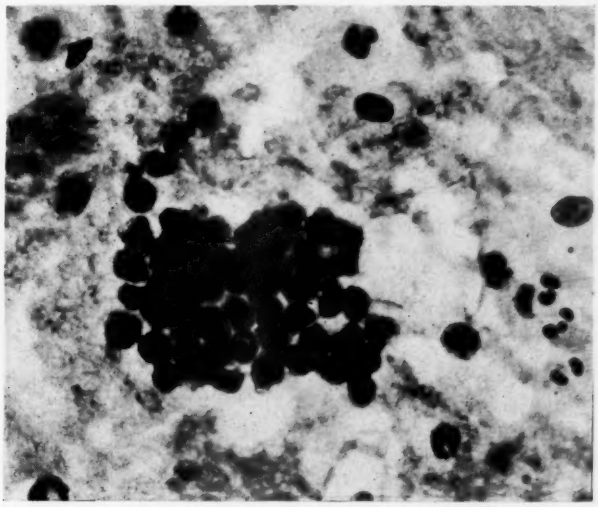

Fig. 12.—Cluster of normal endometrial cells. Menstruation. ×800.

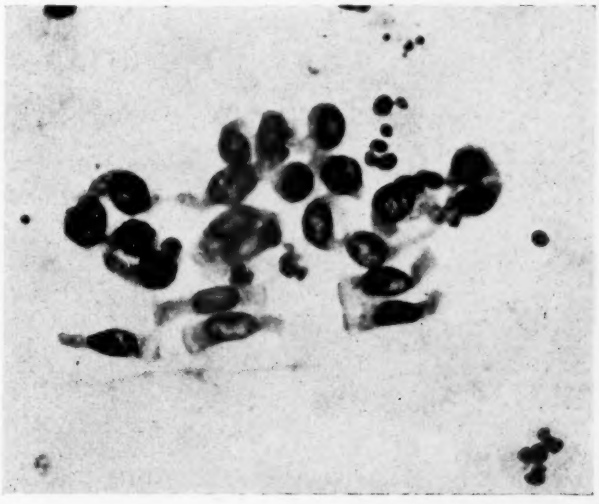

Fig. 13.—Abnormal cell group. Adenocarcinoma of fundus. ×800.

groups which are very characteristic. Degenerating forms are not infrequent. Eosinophiles which are rarely found in normal smears are more frequently seen in malignancy, though in small numbers. Leucocytes in general have a somewhat limited diagnostic value because their number undergoes great fluctuations under different conditions.

It is also affected by the presence of certain bacterial forms. The bacterial flora in cervical malignancies is usually rich and consists of various types with cocci and diplococci predominating. Trichomonas and chronic inflammatory infections may cause considerable leucocytosis.

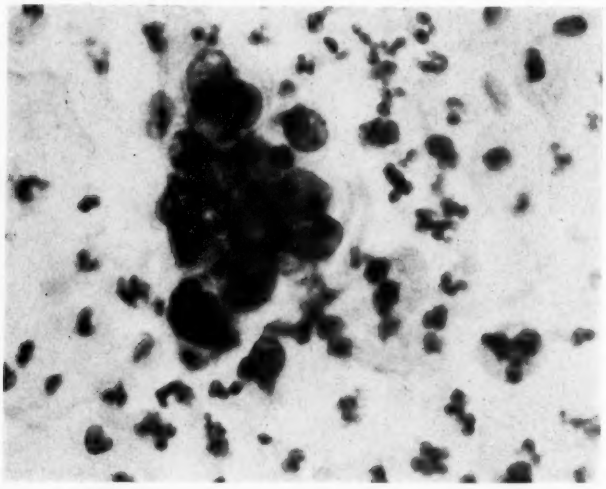

Fig. 14.—Abnormal cell group. Adenocarcinoma of fundus. ×800.

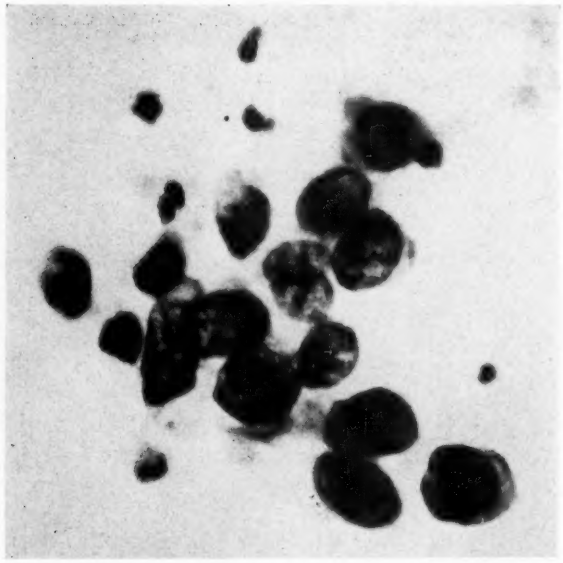

Fig. 15.—Abnormal cell groups. Adenocarcinoma of fundus. ×800.

The histiocytes deserve special consideration. They are invariably present in carcinoma smears and usually display a high phagocytic activity. They phagocytize dead leucocytes, erythrocytes, and other cellular debris. They appear single or in groups. Their size varies greatly. The larger ones reach the size of small epithelial cells with which they

may often be confused. Their cytoplasm is vacuolated. Some of the vacuoles are large and seem to persist after digestion of engulfed elements (Fig. 11). Their nuclei tend to grow and to become hyperchromatic. Histiocytes with more than one nucleus may be seen. A good many undergo degeneration. The cytoplasm and nucleus both become pyknotic. After ingestion of erythrocytes, the cytoplasm often becomes acidophilic and stains red with eosin. The number of degenerating histiocytes appears to be relatively high.

DESCRIPTION OF SMEARS SHOWING ADENOCARCINOMA OF FUNDUS

The general characteristics of the vaginal smear of adenocarcinoma of the fundus are in many ways similar to those of carcinoma of the cervix. The prevailing types of "aberrant" cells are, however, of different origin. They are derived from the endometrium, and are carried

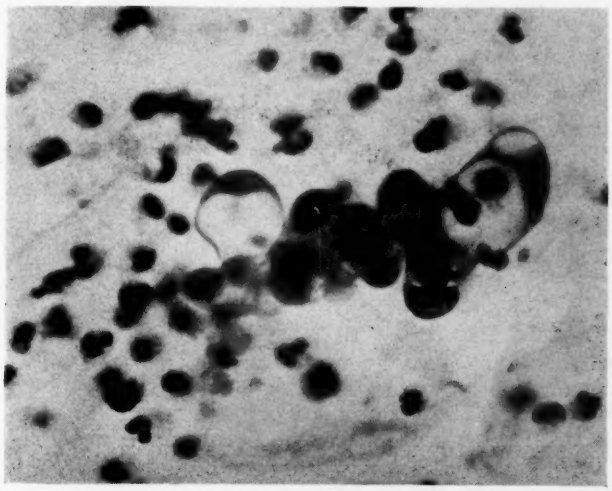

Fig. 16.—Abnormal cell group including some large histiocytes. Adenocarcinoma of fundus. ×800.

into the vagina by the uterine bloody discharge. They do not show the high variability displayed by the modified squamous epithelial cells found in cervical carcinomas. They are considerably smaller and their variations in size and form are more limited.

The most frequently found cell types have a cuboidal, columnar, or spindlelike form and appear singly or in dark-staining clusters, which can be easily spotted with low power (Fig. 13; compare with Fig. 12). Some cells become elongated, or rounded, and show some resemblance to cells found in carcinomas of the cervix. Sometimes the cells are so densely grouped together that their outlines become very indistinct (Fig. 14). Vacuolated cells are not infrequent. A very characteristic cell type is one that has a large vacuole which is often filled with dead leucocytes or with cell debris. Such cells are evidently of histiocytic nature and perform a phagocytic action. They appear single, grouped, or intermixed with the uterine cells (Figs. 16 and 17).

The nuclei tend to be hyperchromatic and show marked variations in size (Figs. 14 to 17). Some are considerably enlarged (Fig. 15). They generally have an oval or rounded shape, and their chromatin is distributed in the form of conspicuous dark-staining granules. The cells are sometimes plasmolyzed and the nuclei are set free. Such nuclei appear single or in irregular clusters and are very characteristic.

The blood cells and the histiocytes show the same reactions as in carcinomas of the cervix. The histiocytes are, as a rule, numerous and display a high phagocytic activity.

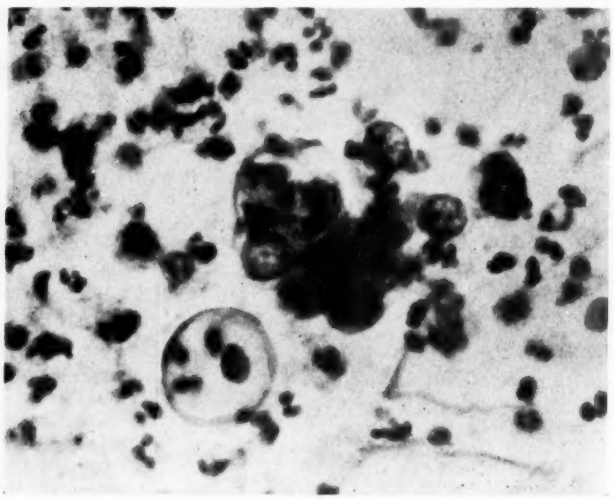

Fig. 17.—Abnormal cell group including one large histiocyte. Adenocarcinoma of fundus. ×800.

SMEAR REACTIONS IN CARCINOMAS OF OTHER ORGANS OF THE FEMALE GENITAL TRACT

Carcinomas of the vagina or vulva are characterized by large, abnormal basal and superficial squamous cells, some of which are cornified. Unusually large cornified cells with highly aberrant forms and enlarged or fragmented nuclei are particularly frequent. In malignant tumors of the ovary, the findings have not been consistent. In some cases the vaginal smears showed no deviations from the normal. In others, some atypical cells have been noticed, the nature of which is somewhat obscure. It is very likely that such cells are not derived from the ovarian tumor, but from possible metastatic lesions of the uterus. The number of the cases studied up to the present is too small to permit definite conclusions.

DISCUSSION

It will be seen from the foregoing descriptions that the interpretation of the smear depends upon an intimate knowledge of the cytologic characteristics of the vaginal fluid. It may also be inferred that this is a somewhat more difficult matter than the problem presented by the diagnosis of carcinomatous tissues. However, it is safe to say that the

requirements are not above the powers of any trained cytologist or pathologist after these have had adequate training and sufficient experience. From our experience it should be said that in general gynecologic diagnosis, the vaginal smear technique presents greater difficulties than those presented by some of the conditions in which it has been widely used, such as the evaluation of estrogenic effect upon the vaginal epithelium.[5]

During the past two years we have collected and studied many hundreds of vaginal smears from normal women and those suffering from gynecologic disease, and we feel that cells pathognomonic of cervical and fundal carcinoma can be definitely recognized. We are not yet in a position to offer a statistical proof of the reliability of this method of diagnosis, but we can say that in our experience it yields a high percentage of correct diagnoses when checked by tissue biopsies. There is evidence that a positive diagnosis may also be obtained in some cases of early disease. The simplicity of the method, the lack of inconvenience to the patient during its application and the possibility of obtaining daily information over a long period of time makes it very useful in following the progress of the disease after operative procedures or x-ray treatments.

In presenting this method of diagnosis at this time, we hope that it may prove to be a dependable means whereby the principal malignant diseases of the uterus can be recognized; and further that because of its simplicity, it may eventually be applied widely so that the incipient phases of the disease may come more promptly within the range of our modern modes of treatment which have been proved highly effective in early carcinoma. In conclusion, it may be well to reiterate that whereas the method makes the material for examination easily and frequently obtainable at low cost, the interpretation of the smear requires the services of a careful and discriminating cytologist who has had experience in this field. Few persons can be depended upon for this work at the present time; however, if the method proves to be worthy of further development, as we expect it to be, then it will be possible in a relatively short time to provide the necessary facilities for instruction.

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DISCUSSION

DR. JOSEPH HINSEY (by invitation).—This problem is one that is different from tissue pathology. In tissue pathology we have not only the cytology of the cells involved, but also the orientation of those cells in the tissues. Here we are dealing primarily with the cytology of cells and are faced with problems which are like those of the hematologist who makes his examination of the blood smear.

The interpretations presented here have been possible only through the very broad and long study which Dr. Papanicolaou has made of the cytology of these cells in the female reproductive tract, combined with the knowledge of gynecologic pathology which Dr. Traut possesses.

DR. FRANK R. SMITH.—Any one who has seen a roentgen ray picture of a woman who has recently been curetted and then had lipiodol injected into the uterus and sees the Christmas tree effect of the dissemination of the lipiodol, would be impressed with the dangers of curettage as a method of diagnosis in carcinoma of the body of the uterus. Any method that will eliminate that obvious danger must necessarily be encouraged. At Memorial Hospital we have realized that danger for some time. We have emphasized the fact that the term curettage should be avoided, and we prefer to say that we obtain a biopsy with the curette. The advantage of having a curette or some other instrument to palpate the interior of the uterus is nevertheless not to be overlooked.

DR. HOWARD C. TAYLOR, JR.—This problem has to be met in three steps of which Dr. Traut and Dr. Papanicolaou's presentation is the first. They have succeeded in demonstrating that when certain types of cells are found, cancer is present in the cervix or the fundus of the uterus. That in itself may have considerable practical importance, because in patients in whom there is vaginal bleeding and in whom you suspect cancer of the endocervix or the corpus, you may find these cells. When the test is positive, you may almost assume that cancer is present above the external os.

The next step is the more difficult one. That is to demonstrate that when these cells are not present in the vaginal smear, cancer is not present in the cervix or the endometrium. In other words the value of negative findings in the smear must also be established from a practical standpoint which is an even more important point to establish than the first one.

The third step is to organize medical practice so that these tests may become a routine. It is worth while here to recall the experience which we have had with the Schiller test. This was a practical test, widely written about, supported by prominent gynecologists. Yet I do not think there is any gynecologic clinic which is practicing this test routinely at the present time.

DR. I. C. RUBIN.—Many years ago I had the privilege of showing several cases from the Schottländer laboratory of the von Rosthorn Clinic, Vienna, of incipient carcinoma of the cervix which were only pin point in size and were found in cases of prolapse. The diagnosis was doubted by a number of investigators. Since then the findings in the cases originally presented have been corroborated by Cullen and others, and the slides shown by Drs. Papanicolaou and Traut present the same histologic features.

The question arises as to the extent that this simple vaginal smear method will help us in diagnosing, not the obvious lesions of the cervix, but the deeply-seated carcinoma of the fundus and possibly those rare cases of Fallopian tube carcinoma from which may be shed and discarded some of these malignant cells.

The great value, besides diagnosing fundal carcinoma, is that one can avoid a traumatic curettage. A traumatic biopsy of the cervix may possibly also be avoided. If this proves diagnostic in a large number of cases of the hidden type of carcinoma and of the early, hitherto unrecognizable carcinoma of the cervix by the usual means at our disposal, including the colposcope, then we have made a great advance in the diagnostic armamentarium in this field.

A STUDY OF THE OVARIES AND ENDOMETRIUMS OF PATIENTS WITH FUNDAL CARCINOMAS*

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INTRODUCTION

MANY theories concerning the origin of adenocarcinoma of the endometrium have been postulated. There is, however, no established proof of the direct causative factors of this malignant lesion. The theory relative to the importance of the estrogenic hormone has been based on the interpretation of concomitant ovarian and endometrial findings. The occurrence of follicular cysts, failure of ovulation, and infrequency of corpora lutea, and hyperplasia of the endometrium in patients with adenocarcinomas have been given as proof that hyperestrinism or the unopposed action of estrogen is the immediate cause of the malignancy (Taylor, 1932, 1938; Taylor and Miller, 1938; Herrell, 1939; R. Meyer, 1923; Novak and Yui, 1936; Payne, 1937; Horsley, 1924; Baecker, 1904; and Mazzola, 1938). Herrell (1939) reported the isolation of five rat units of estrin in twenty-four-hour urine specimens in 8 of 10 postmenopausal women with adenocarcinoma. Such quantities of estrin, however, are similar to those found in the urine of normal male and female castrated patients (Frank, Goldberger, and Salmon, 1936; Dingemanse, Borchardt, and Laqueur, 1937).

Taylor, in discussing the etiologic importance of estrogens, reported an instance of adenocarcinoma in association with a granulosa cell tumor of the ovary. In further support of the relationship between estrin and this type of malignancy, Herrell (1939) reported that he had not seen an endometrial carcinoma in a previously castrated patient. Baecker, Taylor, R. Meyer, and Novak and Yui have stressed the relationship between hyperplasia and endometrial carcinoma. Most authors accept the theory that hyperplasia results from unopposed estrogenic effects. Ewing (1928) reported three cases of carcinoma arising in hypertrophic glands, and Bamforth (1931) observed an early carcinoma in hyperplastic endometrium.

That the uninvolved endometrium is not unduly stimulated by the estrogens and is not hyperplastic in type in patients with carcinoma has been shown by TeLinde (1932), Fluhmann and Stephenson (1929), Hintze (1929), Healy (1937), Fluhmann (1936), Burch and others (1934), and Herrell (1939).

It is apparent that the association between hyperplasia and endometrial carcinoma is questionable. The various reports indicate that hyperplasia is not found with any great frequency in patients with carcinoma. It is logical to assume that estrogenic stimulation adequate to cause carcinoma would also stimulate the remaining portions

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of the endometrium to a greater extent than that which is found. Definite proof that hyperplasia is a precursor of carcinoma has not been established.

Since uterine fibroids and endometrial carcinomas are frequent concomitant lesions (Graves, 25.7 per cent; Norris and Vogt, 26.8 per cent), and since fibroids are thought by some to be the result of estrogenic stimulation, it has been assumed by many that carcinoma of the endometrium is the direct result of estrogenic stimulation.

Such findings as these, even if they were not debatable, cannot be used as absolute proof of the etiologic importance of hyperestrinism or the unopposed action of estrin.

Experimental evidence in the rat, mouse, guinea pig, rabbit, and monkey has demonstrated several facts. Estrogens in large quantities given to these animals over prolonged periods of time have produced cystic glandular hyperplasia of the endometrium but in no instance was carcinoma produced. Carcinomatous changes were induced only when some carcinogenic agent was used in conjunction with the estrogenic therapy.

That corpora lutea are occasionally present and apparently normal in patients with endometrial carcinomas has been reported by Taylor (1932) and Herrell (1939). This leads one to conclude that it is possible for ovarian function to be normal in these patients. Definite conclusions, however, are difficult to make, since the number of premenopausal women with such malignancies is relatively small and since such patients rarely have cyclic menstruation.

MATERIAL

The material for this study was obtained from patients with endometrial carcinomas treated at St. Luke's Hospital, Chicago. There were 150 such patients. They were classified into two groups. In one group there were 68 patients who had been treated primarily by surgery and who had received no preoperative irradiation. The other group was composed of 82 patients who had received preoperative irradiation. The latter group was not suitable for this study, because of the possible changes in the ovaries and endometrium produced by such irradiation.

The study is concerned with the histologic and anatomic evidence of function of the ovaries and the endometriums in the presence of endometrial carcinomas. It is logical, therefore, to classify the 68 patients into premenopausal and postmenopausal groups. Nineteen patients were definitely premenopausal. Forty-nine patients were in the postmenopausal group. These latter patients had no bleeding from the uterus for several years, until the onset of the bleeding associated with the carcinoma.

In each instance, the surgical and pathologic studies included accurate measurements and detailed gross and microscopic observations of both ovaries, the complete uterus, the extent of the malignant lesion, and the uninvolved endometrium. The preservation of all of the

paraffin blocks of the surgically removed tissues and the accurate and detailed pathologic records by Dr. Edwin F. Hirsch, Director of the Henry Baird Favill Laboratory, made this study possible.

PREMENOPAUSAL GROUP

The ages of the nineteen patients in this group ranged from 25 to 51 years. There were two between 25 and 29 years of age; two between 30 and 34; four between 35 and 39; six between 40 and 44; and five between 45 and 51 years of age. These patients were having menstrual bleeding in addition, in most instances, to some abnormal bleeding associated with the carcinoma. In 11 of these 19 patients exact dates of the onset and conclusion of the last menstrual periods were established. The remaining 8 patients were unable to state these dates accurately.

Two of the 11 patients who presented definite menstrual dates were operated upon on the fifth and twelfth days of the menstrual cycle, respectively. Nine patients were operated upon between the fourteenth and twenty-fifth days of the cycle (Table I).

Fig. 1.—Patient M. R. A. In this patient the endometrium removed on the eighteenth day of the cycle is progravid.

The two patients operated upon before the thirteenth day had no corpora lutea of the present menstrual cycle. The patient operated upon on the fifth day, however, had a degenerating corpus luteum of the previous cycle. If one agrees with the established fact that ovulation occurs most frequently near the midpoint of the cycle, then the absence of ovulation in these two patients is the expected finding. The portions of the endometriums not involved in the carcinomatous process in these two patients were normal postmenstrual and interval types, respectively. These findings in the endometriums and the ovaries are identical with those demonstrated in completely normal menstruating women.

In the 9 patients operated upon after the fourteenth day of the cycle, the ovaries were removed in six instances and not removed in three. The 3 patients in whom the ovaries were not removed were operated upon on the sixteenth, eighteenth, and twenty-second days of their cycles, respectively. The endometrium in each instance which was not involved in the adenocarcinoma was secretory in character (Fig. 1), indicating that corpora lutea were present and that the response of the endometrium was normal. Although demonstration of the corpora lutea in these

three patients was not possible since the ovaries were not removed, the fact that corpora lutea were present seems well founded on the demonstration of the character of the endometrium.

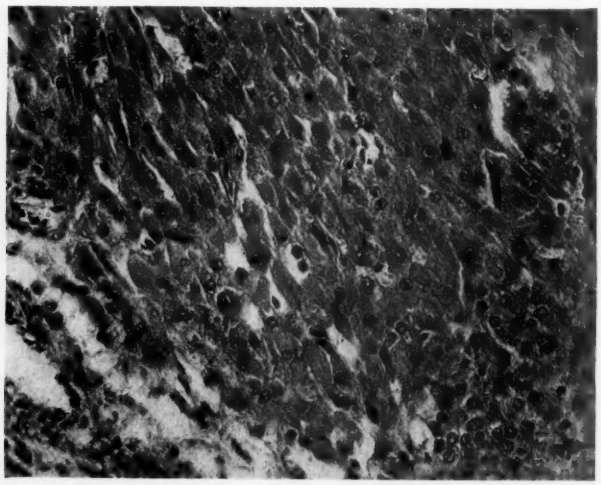

Fig. 2.—Patient L. R. The granulosa lutein cells of the histologically normal corpus luteum in an early vascularization stage are shown. This patient was operated upon on the fourteenth day of the cycle.

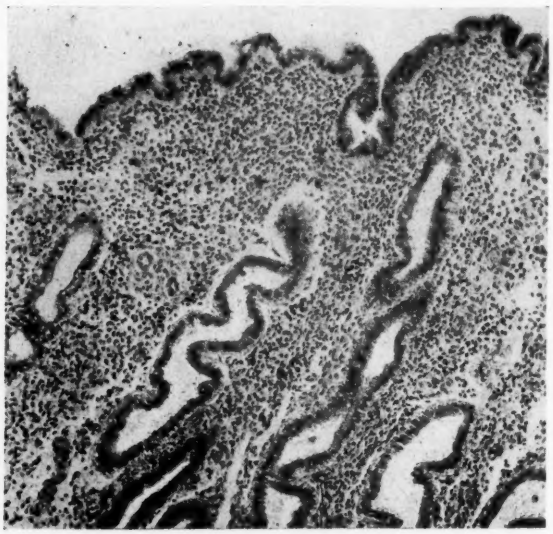

Fig. 3.—Patient L. R. The endometrium in an early progravid stage is consistent in degree of development with that of the corpus luteum. (See Fig. 2.)

In the 6 patients who had the ovaries removed, corpora lutea were present in five. The normal, young corpus luteum removed from Patient L. R. (Table I) on the fourteenth day had a narrow layer of fibroblasts lining the cavity. The granulosa lutein cells were large, luteinized, and contained few fat vacuoles. There was a moderate amount of connective tissue. Small vessels were also present. The theca cells were vacuolated, smaller than the granulosa lutein cells, and were grouped in the angles of the fold of the granulosa lutein layer (Fig. 2). The uninvolved endo-

metrium in this patient was an early, normal, progravid type (Fig. 3). The adenocarcinoma is shown in Fig. 4.

The corpus luteum removed from patient S. S. (Table I) on the twentieth cyclic day was in the vascularization stage and was normal. A moderately thick connective tissue layer lined the cavity (Fig. 5). Precipitated fibrin and numerous erythrocytes

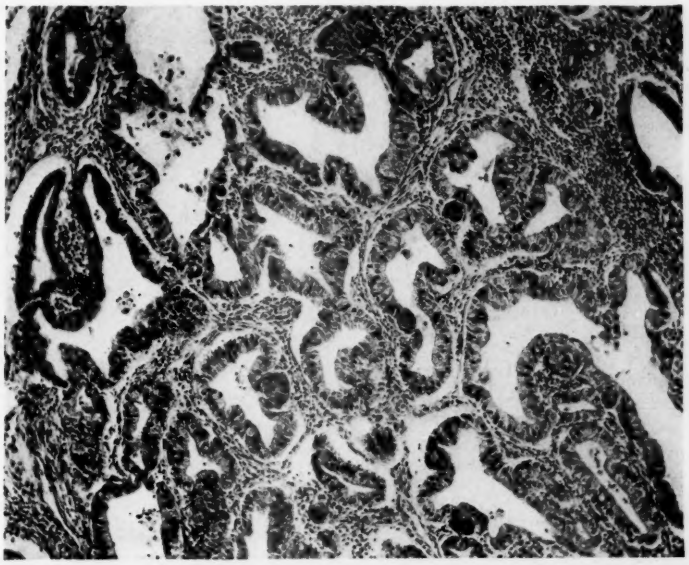

Fig. 4.—Patient L. R. The adenocarcinoma of the endometrium is shown. (See Figs. 2 and 3.)

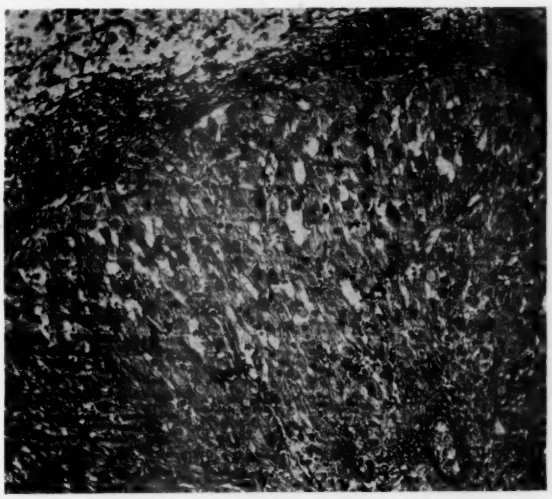

Fig. 5.—Patient S. S. The normal corpus luteum removed on the twentieth day of the cycle is in a vascularization stage.

were intermingled with this layer. The granulosa lutein layer was thick and arranged in typical folds. The cells were large, the cytoplasm stained evenly, and there were few fat vacuoles. The theca cells were typically arranged and were well filled with vacuoles from which lipoids had been dissolved in the process of

fixation. Only small portions of the endometrium were not involved in the malignant growth. These portions, however, were normal and typically progravid in character.

The corpus luteum removed from Patient G. S. (Table I) on the twenty-fifth day was larger than the previous two specimens. It was normal and in the bloom stage. The granulosa lutein layer, however, was more narrow and the characteristic folds were less evident. The individual cells were large, luteinized, and contained some

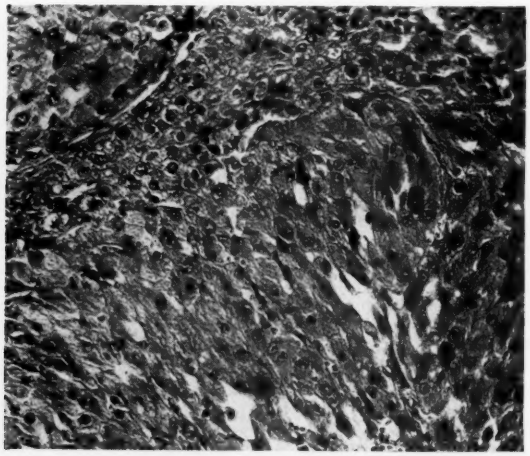

Fig. 6.—Patient L. W. The corpus luteum removed on the eighteenth day of the cycle is in the bloom stage. (See Fig. 7.)

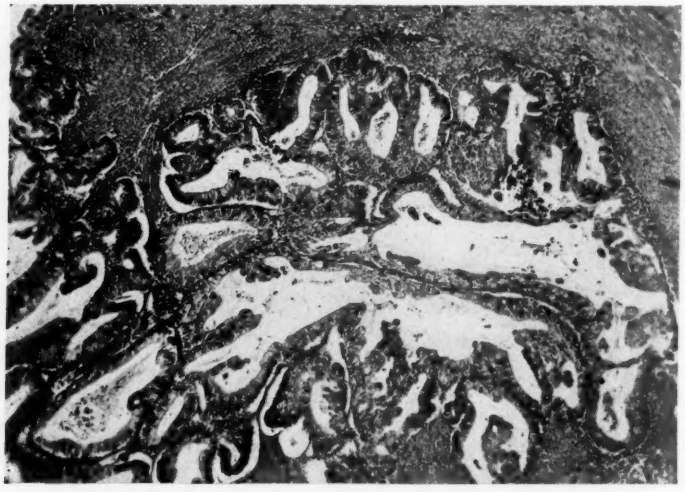

Fig. 7.—Patient L. W. The entire endometrium was involved in the malignant change. Invasion of the myometrium which was extensive is shown.

fat vacuoles. The connective tissue lining of the central cavity was quite thick. The theca cells were scattered more or less evenly about the periphery and were highly vacuolated. The normal endometrium was late progravid. The spiral arteries extended to the surface epithelium where branchings were numerous.

The normal, young corpus luteum removed from Patient L. W. on the eighteenth day of the menstrual cycle had a well luteinized granulosa cell layer which was markedly convoluted. Ingrown connective tissue and small vessels were not numerous (Fig. 6). A narrow layer of connective tissue lined the central cavity. There

were few vacuoles in the granulosa lutein cells. The theca cells, containing frequent large vacuoles, were grouped in the angles of the folds of the granulosa lutein layer. The entire endometrium had undergone malignant change and had invaded the myometrium (Fig. 7).

The normal corpus luteum removed from Patient M. C., aged 51 years, on the twenty-fourth day was in the bloom stage and had a fully luteinized granulosa lutein cell layer. There was a thick connective tissue layer lining the central cavity. Many of the granulosa lutein cells contained peripherally arranged vacuoles. There was extensive vacuolization of the theca lutein cells. The endometrial carcinoma was so extensive that all the endometrium was involved. The myometrium was invaded.

TABLE I. PREMENOPAUSAL PATIENTS (19)

	NAME	AGE	CYCLE DAY OF OPERATION	CORPUS LUTEUM	ENDOMETRIUM
First half of cycle	M. A.	34	5	0	Postmenstrual
	V. C.	38	12	0	Proliferative
Second half of cycle	L. R.	42	14	+	Progravid
	R. G.	40	16	Ovary not removed	Progravid
	M. R. A.	39	18	Ovary not removed	Progravid
	L. W.	46	18	+	All carcinoma
	S. S.	30	20	+	Progravid
	J. N.	37	21	0	Proliferative
	I. C.	44	22	Ovary not removed	Progravid
	M. C.	51	24	+	All carcinoma
	G. S.	37	25	+	Progravid

The remaining patient, J. N. (Table I), was operated upon on the twenty-first day of the menstrual cycle. There was no corpus luteum present. The ovaries were 3 by 3 by 1.8 and 2.5 by 1.5 by 1 cm. in size. The ovaries contained no large follicles and no cysts. The endometrium not involved in the malignant growth was interval in type. The development was identical to that observed in the mid-cycle in the endometrium of a normal woman. This patient is the only one of this group who had not ovulated by the middle of the cycle.

The 5 corpora lutea described above are histologically normal. Their degrees of development at the time of their surgical removal are similar to that of corpora lutea removed at corresponding times from completely normal menstruating women. That three of these corpora lutea are functioning in a normal manner is evidenced by the normal and characteristic responses they have elicited in the endometriums. Demonstration of the normal function of the other two corpora lutea, as determined by a study of the endometria, could not be made since the entire endometrium in both instances had undergone malignant change. In spite of the absence of any normal endometrium, the corpora lutea were normal histologically. The development of these corpora lutea was similar to that of corpora lutea removed at similar stages in the menstrual cycle from normal women. There is evidence in these two instances to indicate that endometrium is not necessary for the normal development of the corpus luteum.

The endometrium in these instances which is not involved in the carcinoma has the ability and does respond in an entirely normal manner to the follicular and corpus luteum hormonal stimulation that it receives.

So-called cystic glandular hyperplasia of the endometrium was not present in the 11 premenopausal patients who had normal cyclic menstruation.

A group of 8 premenopausal patients could not state with accuracy the dates of their last menstrual periods because of continued and profuse bleeding of various degrees (Table II). In one instance the tissues of the ovary and normal endometrium were not available for study. No corpora lutea were present in the ovaries of the remaining 7 patients.

The endometrium in two instances was characteristic of that described as cystic glandular hyperplasia (Table II). In one patient, R. S., the hyperplasia was

TABLE II. PREMENSTRUAL PATIENTS

	NAME	AGE	CYCLE DATE	CORPUS LUTEUM	ENDOMETRIUM
No cyclic menstruation	M. R. E.	25	?	0	Proliferative
	M. D.	29	?	0	Cystic hyperplasia
	P. F.	40	?	0	Proliferative
	M. T.	41	?	0	All carcinoma
	C. L.	41	?	0	All carcinoma
	R. S.	45	?	0	Cystic hyperplasia
	E. G.	48	?	0	Proliferative
	M. L.	45	?	?	All of tissues not available

extensive while in the other, M. D., it was only moderate. In three instances the endometrium was similar to that of a normal interval type. There was no evidence in these three of any excessive follicular hormonal stimulation. The entire endometrium in two patients was involved in the malignant process.

In the 49 patients comprising the postmenopausal group the ovaries were uniformly smaller than in the patients of the premenopausal group. There were no follicles in the great majority of instances. In only one instance was there a cyst of the ovary. The stroma of the cortex was dense. The medullar region in most contained numerous corpora albicans.

The endometrium not involved in the malignant change, in all but a few instances, was atrophic. In some patients this endometrium was more stimulated than is usual in postmenopausal patients. The ovaries in these patients, however, were atrophic and without follicles.

PATIENTS WITH CYSTIC OVARIES AND ENDOMETRIAL CARCINOMAS

Of the 68 patients studied here, 9 patients had cystic ovaries. Eight of these were premenopausal and one was postmenopausal (Table III). Patient M. A., aged 34 years, had in one ovary a 20 cm. pseudomucinous cystadenoma and in the other ovary a single 4 cm. follicular cyst. This patient had regular menstrual cycles and was operated upon on the fifth cyclic day. The endometrium was a normal postmenstrual type. No excessive stimulation was evident in the uninvolved portions.

Patient L. W., aged 46 years, was operated upon on the seventeenth day of her regular menstrual cycle. The ovaries were normal in size and contained three follicular cysts, the largest 1.5 cm. in diameter. A histologically normal corpus luteum was present (Fig. 6). The entire endometrium had been converted into a malignant growth.

Patient S. S., aged 30 years, had regular menstrual cycles and was operated upon on the twentieth day of the cycle. The ovaries were enlarged (Table III) and one contained four follicular cysts, 1.5 cm. in diameter, and the other ovary had a single 8.5 cm. follicular cyst. There was a histologically and functionally normal corpus luteum in the vascularization stage in one ovary (Fig. 5). The uninvolved endometrium was early progravid.

Patient G. S., aged 37 years, was operated upon on the twenty-fifth day of her regular menstrual cycle. The ovaries were slightly larger than normal (Table III). There were three follicular cysts, the largest 6.5 cm. in diameter. The corpus luteum was normal. The endometrium was a normal progravid type. As in the previous specimens, there were no excessive stimulation effects.

The follicular cysts in the ovaries of these 4 patients were not large and were not numerous. In 3 of the patients in whom some uninvolved endometrium was present, there was no evidence that these follicular cysts had produced excessive endometrial stimulation. Another fact that indicates little or no disturbance of ovarian function was the presence of normally developed corpora lutea in the three patients operated upon after the midcycle (Fig. 5). There was no functioning corpus

TABLE III. PATIENTS WITH OVARIAN CYSTS (9)

	NAME	AGE	CYCLE DAY	OVARIES CM.	CYSTS NO.	CYSTS SIZE	CYSTS TYPE	CORPUS LUTEUM	ENDOMETRIUM
Premenopausal	M. A.	34	5	20 5.5 × 5 × 1.5	1 1	20 cm. 4 cm.	Pseudomucinous Follicular	0	Postmenstrual
	L. W.	46	17	4 × 3 × 1 3 × 1.5 × 1.8	2 1	1.5 cm.	Follicular	+	All carcinoma
	S. S.	30	20	8 × 6.5 × 6.5 8.5	4 1	1.5 cm. 8.5 cm.	Follicular	+	Progravid
	G. S.	37	25	6.5 × 4 × 3.5 7 × 5 × 4	1 2	6.5 cm. 2.4 cm.	Follicular Follicular	+	Progravid
	M. R. E.	25	?	5.5 × 4 × 2.5 5.5 × 3.5 × 3	8	1 cm.	Follicular	0	Proliferative
	M. D.	29	?	6.5 × 5 × 3 2 × 2 × 1	3 0	2 cm.	Follicular	0	Cystic hyperplasia
	R. S.	45	?	4 × 3.5 × 2.8 3.5 × 2 × 1	1 0	3 cm.	Follicular	0	Cystic hyperplasia
	M. L.	45	?	6 × 3 × 2.4 6.5 × 6 × 4	1	Metastatic adenocarcinoma 5 cm.	Follicular	1	All of tissue not available
Postmenopausal	B. M.	47		10 × 9.5 8.5 × 7 × 4	1 1	10 cm. 3.5 cm.	Papillary cystadenoma Follicular	0	Slight proliferative

luteum found in the ovaries of the other patient since she was operated upon immediately postmenstrually, on the fifth day of the cycle.

That there has been no excessive estrogenic stimulation associated with the follicular cysts in these patients is indicated by: (1) The uninvolved endometrium has responded in a typical manner to normal estrogenic and corpus luteum hormone stimulation; and (2) the occurrence of ovulation and completely normal corpus luteum development and function.

The following 4 patients (Table III) are premenopausal women who had had no regular menstruation (Table III).

In patient M. R. E., aged 25 years, the ovaries were slightly enlarged and contained eight follicular cysts 1 cm. in diameter. The endometrium was proliferative in type without excessive growth. There was no corpus luteum in the ovaries.

In Patient M. D., aged 29 years, one ovary was slightly enlarged and contained three follicular cysts, 2 cm. in diameter. The other ovary was small and contained no cysts. The endometrium was characteristic of a moderate, so-called, cystic glandular hyperplasia. No corpus luteum was present.

The ovaries of Patient R. S., aged 45 years, were normal in size and contained but a single 3 cm. follicular cyst. The ovaries did not contain a corpus luteum. The endometrium evidenced marked, so-called, cystic glandular hyperplasia.

In Patient M. L., aged 45 years, the ovaries were larger than normal. In one there was a single 5 cm. follicular cyst and in the other there was a metastatic adenocarcinoma. The endometrial tissues were not available for this study.

The endometrium of two of these three premenopausal patients without cyclic menstruation evidenced the effects of either excessive or prolonged estrogenic stimulation (Table III). The cyclic ovaries found in these patients were histologically no different from those observed in the premenopausal patients with normal cyclic menstruation. The greatest degree of endometrial stimulation was noted in the patient (R. S., Table III) whose ovaries were the smallest in this group and in which there was only one small follicular cyst.

There was only 1 of 49 postmenopausal women who had cystic ovaries (Patient B. M., Table III). She was 47 years of age and had had menopausal symptoms of hot flushes and amenorrhea for only nine months. One ovary was large and contained a 10 cm. papillary cystadenoma. The other ovary was also enlarged and contained one follicular cyst 3.5 cm. in diameter. There was no corpus luteum. The endometrium evidenced slight estrogenic stimulation.

In the postmenopausal women with adenocarcinoma of the endometrium studied here, cystic ovaries were not present except in a single isolated instance. The uninvolved endometrium in these patients evidenced very little estrogenic stimulation and in many there was none.

SUMMARY AND CONCLUSIONS

1. Nineteen of the 68 patients studied were premenopausal. Eleven of these had cyclic menstruation. Nine of these 11 patients were operated upon between the fourteenth and twenty-fifth cyclic days. Eight possessed functioning corpora lutea. The two operated upon before the fourteenth cyclic day had corpora lutea of the previous cycle.

2. The corpora lutea were normal even in those instances in which all of the endometrium was involved in the malignant change.

3. The portion of the endometrium not involved in the malignant change in those patients with corpora lutea was normal and had responded to ovarian stimulation in a normal manner.

4. Cystic glandular hyperplasia was not present in any of the patients with cyclic menstruation.

5. Cystic glandular hyperplasia was found in 2 of the 68 patients comprising this study.

6. Cystic changes in the ovaries were found in 8 premenopausal patients and in one postmenopausal patient.

7. Ovulation and corpus luteum development progressed normally, even in those patients with cystic ovaries.

8. The cystic changes in the ovaries thus were demonstrated to be incidental and without significance.

9. In patients with endometrial carcinomas, the ovaries may function normally and the uninvolved portion of the endometrium may be normal and respond normally to ovarian stimulation.

10. Thus, the etiologic significance of hyperestrinism or the unopposed action of estrin in endometrial carcinoma is not demonstrated in the patients of this report.

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Boisseau, Spinetta, Druelle, and Durandy: The Infrequency of Neurosyphilis in Prostitutes, Presse méd. **47:** 1658, 1939.

The writers, working in the Nice and Maritime Alps Prophylactic Medical Center, saw 1,313 cases of syphilis (287 hereditary and 1,026 acquired cases) in the period between April 1, 1938, and Feb. 15, 1939. In the group of 1,026 cases of acquired syphilis, there were 419 females. Twenty-five (6 per cent) of these women had tabes dorsalis, while in 52 other females neurosyphilis existed as cerebral syphilis (5 cases), hemiplegia (3 cases), oculopupillary disturbances (38 cases), and other nerve involvement in 6 instances.

During this same period the authors also examined 668 prostitutes, and of these 307 (46 per cent) had syphilis. None of the syphilitic prostitutes had tabes dorsalis, while in only 3 instances (1 per cent) was there evidence of oculopupillary involvement.

Age does not seem to explain the infrequency of neurosyphilis in prostitutes. Duration of the disease, as a factor, is difficult to evaluate although 73 of the syphilitic prostitutes were known syphilitics for nine years or more.

The writers conclude that the infrequency of neurosyphilis in a prostitute is due to the fact that such an individual receives early diagnosis and early intensive and prolonged treatment for her syphilitic disease.

Clair E. Folsome.

THECA CELL TUMORS OF THE OVARY*

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THECA cell tumors of the ovary are mesodermal neoplasms, which reproduce the varying histologic patterns of the stroma surrounding the Graafian follicle. They also possess distinctive chemical and biologic properties. First differentiated by Loeffler and Priesel in 1932, they were designated as "fibroma theca cellulari xanthomatodes" because of their lipid content. The initial report covered 6 cases, and 4 additional theca tumors were added in 1934. Melnick and Kanter recorded the first 2 cases in American literature in 1934. Geist reported 5 cases in 1935 and added 6 others in 1938. Patterson and McCullagh, Fischer, Greenhill and Greenblatt, Collins, Varino and Weed, Ruzicka, and Traut and Marchetti also added cases of theca tumors to the rapidly accumulating literature. Dockerty of the Mayo Clinic contributed 10 cases, one with concomitant endometrial carcinoma. Eight additional theca cell tumors are herein reported, one in association with body carcinoma.

Reports of theca cell tumors stimulated early interest in their histogenesis. Geist, Gaines, and Pollack experimentally produced luteinized theca cell and granulosa cell tumors by irradiation of the ovaries of mice and concluded that genetically the theca and granulosa cells have a common origin from the parent mesenchyme of the ovary. This concept is in accord with Fischel's recent embryologic studies. It is further supported by Corner's observation that in South American monkeys, the theca interna cell cannot be differentiated from the lutein and interstitial cell of the ovary. In 61 tumors of Graafian follicle origin (granulosa and theca cell types), Traut and Marchetti generally found an admixture of theca and granulosa cells, recording only 4 pure theca cell tumors. Novak and Gray also identified granulosa cells in theca tumors and proposed a common grouping. Though this is valid from a histogenetic and embryologic standpoint, the theca cell tumor is grossly decidedly different, from the granulosa cell type.

Theca cell tumors are unilateral, firm, solid, and vary greatly in size. In our series they ranged from 8 cm. to 25 cm. in diameter. The external surface though occasionally smooth is more often irregularly lobulated. The color varies from a gray to yellowish brown. On cut section the neoplasm may be circumscribed (Cases 6 and 7). As a rule, it is diffuse presenting a fine fibrillar pattern. Varying sized islands have a diagnostic yellow or yellow ochre color. Such zones may fuse insensibly with adjacent gray white fasciculi or are sharply circumscribed by pearly hyalinized fibrous bands which are prominent in many of the

*Read at a meeting of the Brooklyn Gynecological Society, March 7, 1941.

tumors (Fig. 1). Cystic areas are not uncommonly noted and result from liquefaction necrosis (Cases 2, 3, 4, 7, and 8). In Case 4, the theca cell tumor co-existed with a simple serous cyst and could pass as adenofibroma cysticum. Microscopically, the tumor is composed of concentric, parallel or interdecussating sheaths of broad spindle, fusiform, or polygonal cells (Fig. 2). The latter called "epithelioid type," by Geist

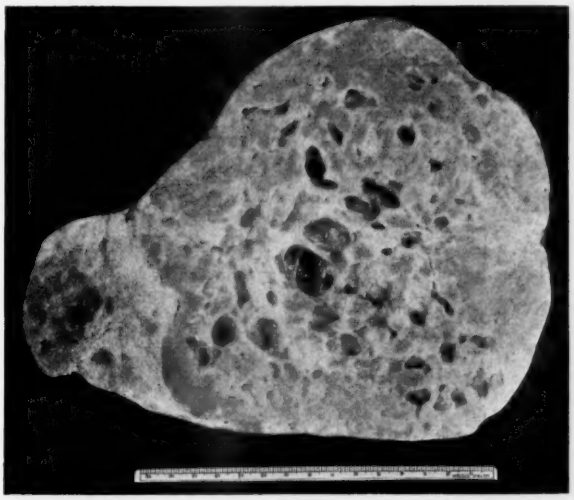

Fig. 1.—Case 2. Gross section of a theca cell tumor. Irregular yellow islands are demarcated by prominent zones of gray white hyaline. A fine reticular matrix is apparent. The numerous cysts are the result of liquefaction necrosis.

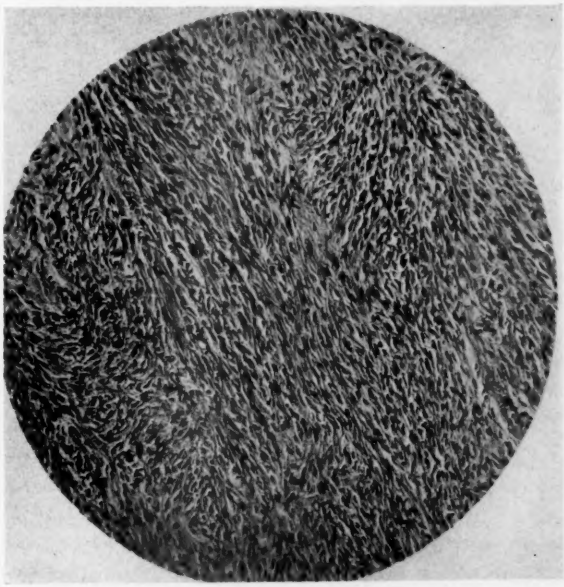

Fig. 2.—Case 2. The theca cells are arranged in broad parallel sheets, irregular whorls or interdecussating irregular angles. The pericellular reticulum is prominent. The cytoplasm is vacuolated. The vesicular nucleus is round, oval or fusiform. There are beginning collagen deposits. ×200.

and Gaines, are often prominent but no constant pattern is present throughout the growth. Adjoining cells are individually separated by connective tissue fibrillae. The cell membrane is poorly defined, the cytoplasm is vacuolated and the nucleus vesicular. Ovoid cell forms simulating the granulosa cell type are inconstant. Hyaline change is frequent and the collagenous matrix supports scattered spindle and fusiform nuclei. In such areas the tumor is indistinguishable from fibromas. Calcareous deposits are not uncommon. By the silver impregnation-staining technique, demarcation of the theca cell by a pericellular fibrous reticulum is especially prominent. This technique also affords differentiation from any contained granulosa cells.

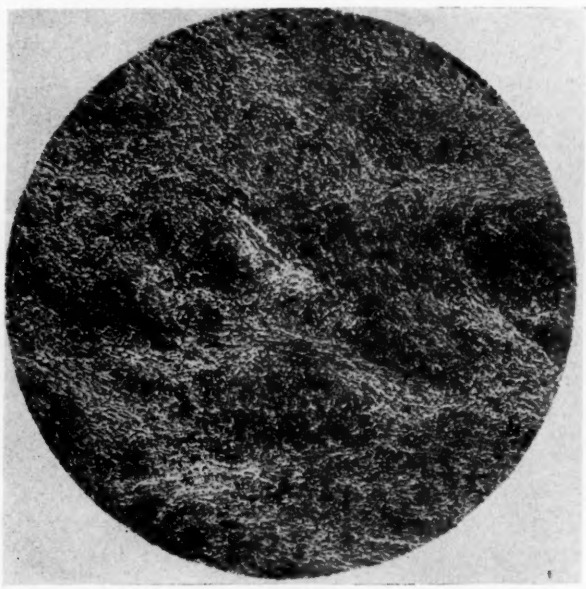

Fig. 3.—Case 1. Theca cell tumor stained by sudan III technique. The collections of dark black granules reveal accumulations of lipid globules in and between the cell bodies. ×80.

Associated pathologic changes in the uterus are noteworthy. The endometrium often shows glandular-cystic or the more active adenomatoid hyperplasia. Occasionally epithelial proliferation is so marked that adenocarcinoma of the body is present. Of 8 cases in this series endometrium was available for study in three. Two showed glandular cystic hyperplasia (Cases 1 and 2), and focal adenocarcinoma coexisted in Case 1. The third case presented a normal premenstrual pattern. Fibromyomas of the uterus were noted in 4 of the 8 cases and adenomyosis interna in 2 of the 3 uteri available for microscopic examination.

The distinctive chemical feature of theca tumor is the content of intracellular and extracellular lipids (Fig. 3). These impart to the tumor its diffuse or more often circumscribed yellow or yellow ochre appearance so diagnostic on gross inspection. By polariscopic examination, Geist first revealed that some of these lipids are doubly refractile, indicating the presence of cholesterol or cholesterol esters. Traut more

recently differentiated the varied lipid components by the osmic acid-sudan III staining technique of Hoerr-Romeis. By this method the minute phospholipid globules stain faint rose pink. The somewhat large globules of free cholesterol appear yellow amber to mahogany. Cholesterol esters, neutral and acid fats appear as larger globules and stain black. This technique was followed in our series and the findings recorded in the individual pathologic reports. It must be emphasized, however, that the amount of lipids is varied in the many zones of the tumor. It is our impression that phospholipids and cholesterol are more marked where the theca cells have a fusiform or rounded appearance. Necrotic areas due to liquefaction or torsion of the tumor show large deposits of acid and neutral fat. With exceptions noted below, other ovarian neoplasms do not contain lipid. In studies of dysgerminoma, fatty acids and neutral fats were noted in areas of necrosis. In the fibrous matrix of a Brenner tumor, studied for comparison, no lipids were present. Phospholipids and cholesterol were diffusely deposited in the cell cytoplasm of three granulosa tumors. Geist and Gaines, Greenblatt, Greenhill and Brown also failed to find lipid deposits in ovarian tumors other than the granulosa cell neoplasm and arrhenoblastoma, both associated with hormonal effects.

The biologic significance of the lipids in theca cell tumors has not been entirely determined, for the function of the normal theca cell has not been fully clarified. Whether lipids are stored in the theca cells or produced in situ is unknown. Geist and Spielman have shown that theca tumors contain large quantities of estrogenic hormone. Chemically, the latter is closely related to cholesterol. It was felt, therefore, that the biologic and hormonal activity of theca tumors might be adjudged by their cholesterol and phospholipid content. An experimental basis for this concept was presented by Bloor, Okey and Corner. Their studies of corpora lutea of the sow indicate that the phospholipid content bears a direct ratio to the physiologic activity of the corpus luteum. The relation of free cholesterol to lutein activity is less clear but appears to be similar to phospholipid. Cholesterol esters appear in high ratio with retrogression of the corpus luteum. Boyd and Elden also analyzing activity of the corpora lutea of the sow conclude that the estrin content parallels the phospholipid concentration. The amount of progestin in the corpus luteum varies inversely with the ratio of free cholesterol which is seemingly converted into hormone.

Traut, Kuder, and Cadden next employed lipid studies to determine the hormonal activity of granulosa and theca cell tumors of the human being. They used the Hoerr-Romeis staining technique and also quantitative chemical analysis for phospholipid, cholesterol, and fats. They concluded that phospholipids are indicative of hormonal potentiality and that neutral fats indicate the end stage of lipid metabolism. In a later communication, however, Traut and Marchetti indicated that pure theca cell tumors, inspite of demonstrable lipid content, may produce no appreciable hormone. They further suggested that the granulosa cells contained in theca cell tumors produced the hormone or else that theca cells produce hormones only in their early stages of growth. The latter view is more in keeping with the known cyclic changes of the

theca cell. In the primordial follicle, it is a spindle fibrous cell changing to an ovoid pseudoepithelial cell with cavitation of the maturing follicle. As shown by Aschheim it contains estrogenic hormone. After follicular rupture and the appearance of the lutein column, the theca cell shrinks, its cytoplasm becomes clear, and the nucleus pyknotic. It reverts to the inactive fibrous stromal cell in the fatty and hyaline involution phases of the corpus and no longer functions. Corner after reviewing all experiments recorded in the literature states "that estrogenic hormone is produced in the ovary and that the most probable site is the theca interna of follicles of all sizes." Allen in a more recent review on the physiology of the ovaries states, "that all ovarian tissue may secrete estrogen-granulosa, theca, interstitial and luteal, although follicular epithelium is normally the primary source."

Our own lipid studies by the differential Hoerr-Romeis staining technique indicate a relationship between high phospholipid and cholesterol content of theca tumors and menstrual anomalies which are clinical indices to hormonal aberrations. The endometrium when available gives further aid in this direction. This method, however, is not entirely accurate, for the source of hormone from any contained granulosa cells is not excluded. The ratio of phospholipid to cholesterol is decidedly varied through the tumor and is difficult to estimate adequately, unless huge numbers of blocks and sections are studied. A small tumor even if abundantly laden with lipids may not produce a total amount of hormone sufficient to evoke endometrial changes or menstrual anomalies. Hyalinized senescent tumors contain little or no lipids. In Cases 1, 3, 7, and 8), which presented menstrual anomalies, there was either diffuse or focal concentration of lipids in the sections examined. The endometrium available in Case 1 showed glandular cystic hyperplasia and focal adenocarcinoma. In Case 2, postmenopausal bleeding was lacking in spite of a glandular cystic endometrium and diffuse lipid content. Evidently this represented the amenorrheic form of hyperplasia. In Case 4, the large but markedly hyalinized tumor with scant lipid produced no menstrual aberrations. Case 5, with scant lipid content, presented menorrhagia, probably due to associated fibroids, for there were no glandular cystic changes in the endometrium. In Case 6, with only mild menorrhagia, there was abundant lipid but the tumor was small in size. The endometrium was not available for study.

The clinical features of theca cell tumors are distinctive but generally similar to those seen in granulosa cell neoplasms. They are usually encountered in women past menopausal age, although no period during active sex life is exempt. Patterson and McCullagh record a theca cell tumor in a 92-year-old woman who complained of vaginal bleeding. The removed uterus showed associated glandular cystic hyperplasia. In our series, the ages ranged from 30 to 63 years, the average was 45 years. Five were multiparas and 3 nulliparas. Menstrual anomalies comprise the most striking complaint. In women past the menopause, there is often recurrent bleeding, but it may be lacking even when glandular cystic hyperplasia is noted. In younger patients, the history is usually of menorrhagia followed by or preceded by amenorrhea or hypomenorrhea. In this series, one of three postmenopausal women experienced

vaginal bleeding (Case 1). In two 45-year-old women, oligo- and hypomenorrhea, respectively, were present (Cases 3 and 8). Of three women in active sex life, two complained of slight menorrhagia (Cases 5 and 6) and one of hypomenorrhea (Case 7). Abdominal pain was a predominant complaint in 7 of 8 cases. In four patients (Cases 3, 5, 7, and 8), this was due to complete or partial torsion of the pedicle. Physical examination generally revealed a firm, ovoid tumor mass. In 6 of 8 cases, this was noted on palpation of the abdomen. In the remaining 2, it was discovered by vaginal touch. A diagnosis of ovarian tumor, however, was made preoperatively only in 3 cases, the remaining 5 were interpreted as fibromyomas. It must be explained, however, that in 3 of these patients the theca cell tumor was associated with fibromyomas of the uterus. Theca cell tumors are usually benign, but the true incidence of malignancy remains to be established. A malignant theca tumor associated with ascites and metastasis has been reported by Loeffler and Priesel. Another malignant theca tumor with ascites was presented by Geist and Gaines. In this report all 8 theca tumors were benign although one was associated with adenocarcinoma of the body. Therapy consists in operative removal of the neoplasm.

CASE REPORTS

CASE 1.—Mrs. J. R. (No. 30846), aged 57 years, white, married, gravida 0, was admitted to the Long Island College Hospital on Aug. 8, 1936, complaining of leucorrhea and vaginal bleeding. Menses began at 13½ years, recurred every twenty-eight to thirty-nine days, and lasted four days. Since October, 1933, however, the periods have been very irregular, appearing at two- to twelve-month intervals. On May 14, 1936, the patient noted yellow or sanquineous vaginal discharge which had persisted until admission. The pertinent physical finding was an irregular nodular uterine mass approximating the size of a fourteen to sixteen weeks' gestation. A diagnosis of uterine fibroid and adenocarcinoma of the fundus was made. At operation there was a small quantity of clear serous fluid in the peritoneal cavity. Panhysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful.

Pathologic Report.—The uterus, removed by panhysterectomy, measured 12 cm. in length, 12 cm. transversely and 7 cm. in the anteroposterior diameter. Enlargement resulted from numerous interstitial fibromyomas, the largest of which in the right cornual region measured 5 cm. in diameter. The cervix was essentially negative. The endometrium was thickened and several fundal polyps were present. The myometrium contained numerous minute fibromyomas. Microscopically, the endometrium presented classical glandular cystic hyperplasia (Fig. 4). In several areas, however, the hypertrophied glands contained proliferating cell buds which fused, resulting in formation of secondary gland spaces (Fig. 5). In such areas cell alignment had been lost. The cytoplasm was reduced in amount and the nuclei varied slightly in size, shape, and staining character. Mitotic figures were common. The stroma was compact and cellular. The myometrium was free from malignant deposits. The fibroids presented the usual appearance. The right and left tubes showed no gross or microscopic anomalies. The left ovary was atrophic.

The right ovary was converted into a firm, lobular mass which measured 13 by 8 by 6 cm. Gross section revealed a fibrillar gray white structure of irregular pattern. Circumscribed islands presented a yellow tint. Microscopically, the tumor was comprised of proliferating broad spindle cells. Deposition of intercellular hyaline was focally pronounced, and calcareous deposits occasionally encountered. Where cellularity was most marked, the spindle cells coursed in irregular sheaths which interdecussated at irregular angles. Broader fusiform cells were frequent. The cell membranes were often indistinct. The nuclei, spindle, oval, or fusiform in shape, were vesicular in character. Nucleoli were prominent. The capillaries were

numerous and often of sinusoidal dimension. The sudan III stains showed fine globules of fat in the bodies of many of the cells as also in some of the intercellular spaces. Distribution was not uniform. Sections stained by the Hoerr-Romeis method confirmed the above. Though there was a moderate amount of phospholipid; brown cholesterol granules were predominant. There were scattered amounts of neutral and acid fat.

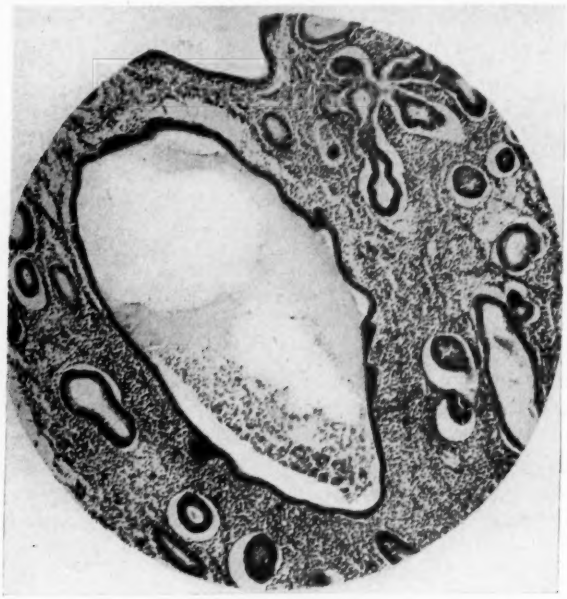

Fig. 4.—Case 1. Classical glandular cystic hyperplasia in association with theca cell tumor of the ovary. ×80.

Fig. 5.—Case 1. Adenocarcinoma of the body associated with endometrial hyperplasia in theca cell tumor. Notice the irregular gland spaces, the proliferating cell buds and secondary gland spaces. Cell alignment has been lost in these more complex glands. The stroma is scant. ×80.

TABLE I. THECA CELL TUMOR. CLINICAL FINDINGS

CASE	AGE AND GRAVIDITY	MENSES	CHIEF COMPLAINT	FINDINGS	PREOPERATIVE DIAGNOSIS	OPERATIVE FINDINGS	OPERATION
2	G. A., 53 Para i	Menopause, 2 yr. No bleeding to date	Enlargement of abdomen, abd. pain, urinary frequency 2 mo.	Irreg. suprapubic mass, size of 5 mo. pregnancy	Fibromyoma of uterus	Fibromyoma of uterus, tumor of left ovary	Supracervical hysterectomy. Left salpingo-oophorectomy
3	M. V., 45 Para vi	14 × 28-35 × 3. In last yr., flow lasts only 1-2 days	Lower abd. pain, nausea constipation 4 days	Supra pubic mass extending to umbilicus. Uterus small, crowded to right	Solid rt. ovarian neoplasm with torsion	4 ounces of free fluid. Torsion of solid rt. ovarian tumor	Rt. salpingo-oophorectomy
4	S. C., 63 Para v	Menopause, 16 yr. No bleeding to date	Lower abd. pain, urinary frequency 1 mo.	Suprapubic mass extending to umbilicus	Fibromyomas of uterus	6 ounces of free fluid. Uterus small, solid left ovarian tumor	Left salpingo-oophorectomy
5	H. D., 38 Grav. 0	12 × 28 × 5, mod. profuse	Severe lower abd. pain, nausea 1 day	Uterus, irregular, size of 4 mo. preg. Mass in cul-de-sac	Fibromyomas of uterus with degeneration	Fibromyoma of uterus, solid rt. ovarian tumor with torsion	Supracervical hysterectomy, bilat. salpingo-oophorectomy
6	F. B., 31 Para ii	12 × 25-28 × 5-6	Pain in R.L.Q., backache 10 days	Uterus normal, firm mass in rt. fornix	Solid rt. ovarian tumor	100 c.c. straw-colored fluid, uterus small, fibroid nodule on ant. wall. Solid tumor of rt. ovary with torsion	Rt. salpingo-oophorectomy. Myomectomy
7	H. F., 30 Para i	13 × 28 × 3. In last yr., flow only 15 hr., scant, muddy	Pain in R.L.Q., 1 yr.	Uterus normal. Mass, size of orange, in rt. fornix	Rt. ovarian cystoma	Uterus and left adnexa normal. Rt. ovarian tumor with partial twist	Rt. salpingo-oophorectomy
8	S. H., 45 Grav. 0	Scant and irreg. menses for several mo., previously regular	Pain in L.L.Q. 1 day	Suprapubic mass extending 2 fingers above umbilicus	Fibromyoma of uterus	Straw-colored fluid in peritoneal cavity. Uterus and rt. adnexa normal, left ovarian tumor with torsion	Left oophorectomy

TABLE II. THECA CELL TUMOR. PATHOLOGIC FINDINGS

CASE	UTERUS	OVARY				
		GROSS	MICROSCOPIC	SUDAN III	HOERR-ROMEIS	SILVER STAIN
2	Multiple fibroids. Glandular cystic hyperplasia. Endometrial polyps. Adenomyosis interna	25 × 20 × 12 cm., wt. 2,612 gm. Firm, circumscribed yellow zones, focal liquefaction necrosis	Large spindle-shaped cells. Marked intercellular hyaline	Intra- and extracellular lipid generally scant but uniform, focal concentrations present	Phospholipid predominant. Cholesterol moderate. Neutral fat, scant	Broad collagenous bands, focally a fine honeycomb network
3		13 × 10 × 7.5 cm., wt. 554 gm. Firm, yellow gray, islands of yellow tissue	Plump spindle-shaped cells separated by bands of collagen	Intracellular lipid generally scant but uniform, occasional focal concentrations	Phospholipid and cholesterol in equal amounts. Neutral fat, scant	Fine reticulum, occasional broad collagenous strands
4		18 × 15 × 12 cm., wt. 1,350 gm. Firm, gray white, prominent blood vessels on surface, several cystic cavities	Interdecussating sheaths of spindle cells, with intercellular hyaline. Also adenofibroma cysticum	Lipid scant, focal concentrations in cellular areas	Phospholipid, moderate. Cholesterol, predominant. Neutral fat, scant	
5	Multiple fibroids. Adenomyosis interna. Premenstrual endometrium	12 × 8 × 6 cm. Firm, gray white, islands of yellow tissue	Collagen prominent. Occasional cellular areas of spindle cells	Lipids scant, clustered in small areas	Phospholipid, scant. Cholesterol, predominant. Neutral fat, rare	Fine pericellular reticulum

6	Solitary myoma	8 × 8.5 × 4 cm. Firm, gray white, fibrillar pattern, irregular mottling due to circulatory change. Tumor circumscribed	Areas of edema and interstitial hemorrhage. Sheaths of cells surrounded by fine reticulum. Hyaline in acellular areas	Diffuse lipids	Phospholipid and cholesterol, numerous. Neutral fat, scant	Fine pericellular reticulum
7		9 × 8 × 3.5 cm. Firm, gray white, reticulated appearance many cystic cavities due to liquefaction necrosis	Interdecussating sheaths of spindle and fusiform cells, separated by conn. tissue septa	Focal concentrations of lipid	Phospholipid and cholesterol equal in cellular zones. No neutral fat	Fine reticulum in cellular areas. Broad zones of wavy collagen in acellular areas
8		22 × 17 × 10 cm. Solid segment is gray white, reticulated. Lower cystic segment	Sheaths of cells, interdecussating or arranged in concentric whorls, embedded in hyaline matrix. Edema focally present	Uniform distribution of intracellular lipid	Scant but uniform phospholipid and cholesterol. Neutral fat, scant	

Diagnosis: Endometrial hyperplasia; focal adenocarcinoma, multiple fibromyomas (interstitial), and theca cell tumor of right ovary.

The clinical history, physical and pathologic findings of the remaining 7 cases are abstracted in Tables I and II.

CONCLUSIONS

1. Theca cell tumors arise from the mesenchyme of the ovary and histogenetically are related to granulosa cell neoplasms.

2. A diffuse or more often insular yellow appearance on cut section is distinctive and allows gross differentiation from ovarian fibroma which it otherwise so closely resembles.

3. Microscopically, the tumor is composed of concentric, parallel or interdecussating sheaths of broad spindle, fusiform or polygonal cells each surrounded by fine connective tissue fibrillas. The Foote or Laidlaw silver stains afford easy demonstration of pericellular network.

4. The microscopic demonstration of intracellular lipids is distinctive. Free cholesterol, cholesterol esters, phospholipids, acid, and neutral fats are recognizable by the Hoerr-Romeis staining technique.

5. The quantitative ratios of the varied lipid fractions studied in conjunction with the endometrial pattern afford some index to the biologic activity of the tumor.

6. Eight cases of theca cell tumors are reviewed. Associated uterine pathology is frequent. Glandular cystic hyperplasia, one with adenocarcinoma was present in two of three uteri available for study. Fibromyomas occurred in one-half of the cases.

7. Amenorrhea or atypical menstrual bleeding is the predominant complaint. Pain, if present, is due to torsion or rotation of the tumor.

8. The presence of a unilateral solid pelvic tumor, independent of the uterus and associated with postmenopausal bleeding or menstrual irregularities, is suggestive of a theca cell tumor of the ovary. Granulosa cell neoplasms, however, must be excluded.

Our thanks are hereby extended to Dr. Max Lederer, Director of Laboratories of the Jewish Hospital, for permission to review the pathologic material, and to Drs. L. S. Schwartz, T. S. Welton, I. Tran, and S. Livingston for permission to review their cases.

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THE QUESTION OF GLOMERULAR DAMAGE FOLLOWING TOXEMIA OF PREGNANCY

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MANY posttoxemic women eventually develop hypertension, and we have found that the status at fifty-two months (average) post partum is very definitely correlated with factors which suggest that toxemia causes damage which is associated with the finding of hypertension at this time. (These factors are, particularly, the duration of toxemia and repeated toxemias, Chesley and Somers,[1] Chesley and others[2].) Perhaps these women with high blood pressure at fifty-two months post partum merely have hypertension earlier than they otherwise might. We do believe that some degree of control over the appearance of hypertension after toxemia is possible, but we cannot say whether this control is postponement or prevention.

In seeking the answer to the question of whether toxemia of pregnancy causes vascular-renal damage, one first looks to pathologico-anatomic observations. There are several reports in the literature describing renal changes as found at autopsy some years after the toxic pregnancy (Heynemann,[3] Herrick and Tillman,[4] McKelvey and MacMahon,[5] Zimmerman and Peters[6]). In nearly all of these cases the patients have died of cardiovascular-renal disease after a more or less prolonged course of hypertension. The pathologic findings have usually been those of nephrosclerosis secondary to the hypertensive cardiovascular disease. The significance of these studies is that they establish the usual nature of the posttoxemic hypertension which has been so often miscalled "chronic nephritis." In some cases either true chronic glomerulonephritis or pyelonephritis has been found; these diseases, when found, frequently having antedated the toxic pregnancy. Herrick, Tillman, and Grebenc[7] in 1936 wrote: "To confuse this disease (hypertensive cardiovascular disease—L.C.C.) with nephritis is to be blind to a well and long accepted opinion of the medical clinic and of the pathologic laboratory." Since 1936 Page[8] has adduced strong evidence that there may be a causative renal factor for the high blood pressure found in many cases of hypertensive cardiovascular disease ("essential" or "primary" hypertension). Even though this be true, it seems worth while to differentiate between this disease and chronic nephritis.

The anatomic studies just cited do not answer the question as to what changes, if any, are specifically caused and left by the toxemia of pregnancy.

Glomerular lesions in the acute phase of eclampsia have been described by Löhlein,[9] Fahr,[10] Lubarsch,[11] Bell,[12] Baird and Dunn,[13] and by several others. The typical lesion seems to be a thickening of the basement membrane of the glomerular capillaries, often with an increase in thickness and occasionally in number of endothelial cells. The significant result of these changes is that the lumina of the glomerular capillaries are narrowed.

Presumably these renal vascular changes are caused by, or concomitantly with the toxemia. Do they persist?

Bell described old glomerular lesions in a woman dying of recurrent eclampsia seven years after the original attack. He considered that such lesions do persist, and that the posttoxemic hypertension, so often found, might be explicable on this basis. Baird and Dunn did not find the same lesion persisting eighteen months after eclampsia, in the one case which they examined after an interval. Page and Cox[14] have added observations on 7 more patients dying of various causes at different times after toxemia of pregnancy. In all cases they found some degree of thickening in the glomerular basement membranes, which they believed to have persisted as a sequela of toxemia. Kellar, Arnott and Matthew[15] did not examine any cases surviving the acute toxemia, but thought that it is "not unreasonable to suppose that in a certain number of cases the lesion will progress and develop into a fully established chronic nephritis." However, Kellar[16] later failed to find such changes in the kidneys of 3 women dying of recurrent toxemia.

Since the glomerular lesions might gradually heal, even in the presence of hypertension, the ideal material for pathologic study would be the kidneys of women dying accidentally a few months or a very few years after the toxemia of pregnancy. As we have seen, such observations are very few, and these are contradictory. We have, therefore, attempted an in vivo "chemical dissection" of the kidney in a series of posttoxemic women. These observations on the renal and glomerular hemodynamics may be interpreted as supporting the hypothesis that toxemia of pregnancy does leave renal-vascular damage. Perhaps this damage may initiate the vicious cycle causing hypertension.

METHOD

Smith, Goldring, and Chasis[17] have found that, at low plasma concentrations, diodrast has a renal extraction ratio of very nearly 100 per cent. That is, however much goes in the renal artery none comes out the renal vein, because all the diodrast is removed (and excreted) on one perfusion of the kidny. Measurement of the blood level of diodrast and of the quantity excreted each minute, then, enables one to calculate the volume of plasma (or whole blood) which must have perfused the kidney to provide the diodrast excreted.

The volume of glomerular filtration may be measured simultaneously by determination of the ratio of the quantity of inulin excreted each minute to the plasma level of inulin, since inulin is neither excreted nor reabsorbed by the renal tubule cells (Smith[18]). Also, the volume of filtrate may be approximated from the maximal urea clearance. Usually the maximal urea clearance, in milliliters per minute, is about 60 per cent of the glomerular filtration.

Simultaneous measurement of the plasma flow (diodrast clearance) and glomerular filtration (inulin clearance or $\frac{\text{urea clearance}}{0.60}$) permits us to calculate what proportion of plasma is filtered into Bowman's capsule as "pre-urine." This is a most useful calculation, and the quotient of $\frac{\text{glomerular filtration}}{\text{plasma flow}}$ is called the "filtration fraction."

RESULTS AND DISCUSSION

In Table I are summarized the observations made in 30 normal women, and in 11 hypertensive women who have never had a toxic pregnancy. Normally the filtration averages about 116 ml. per minute, the renal plasma flow averages 567 ml. per minute, and the filtration

fraction is about 20 per cent. In the hypertensive women who have had no pregnancies or no toxemias of pregnancy, the renal blood flow is characteristically reduced while the filtration remains relatively normal because of the high filtration fraction. These changes have been described as typical for essential hypertension in men, and to avoid circumlocution we shall refer to these patients as having the "male type" of hypertension.

TABLE I. SUMMARY OF OBSERVATIONS ON RENAL HEMODYNAMICS IN NORMAL WOMEN, AND IN HYPERTENSIVE WOMEN WHO HAVE NEVER HAD A TOXEMIA OF PREGNANCY. COMPLETE DATA FOR EACH CASE HAVE BEEN PUBLISHED ELSEWHERE (CHESLEY AND CHESLEY[19])

CASES	MEAN AND RANGE	GLOMERULAR FILTRATION ML./MIN.	PLASMA FLOW ML./MIN.	FILTRATION FRACTION PER CENT	RENAL BLOOD FLOW ML./MIN.	DEFICIT IN BLOOD FLOW PER CENT
			Normal Women			
30	Mean	116	567	20.4	850	0
	High	163	848	24.5	1233	
	Low	75	459	15.2	693	18
			"Male Type" Essential Hypertension			
11	Mean	106	351	30.2	559	34
	High	128	557	45.4	685*	19*
	Low	32	96	25.0*	153	82

*Excluding 3 cases with normal renal blood flow; lowest filtration fraction of these 3 is 21.3 per cent, highest renal blood flow is 868 ml. per minute. All cases are included in the means.

It will be remembered that glomerular filtration is a purely physical process dependent upon the intracapillary hydrostatic pressure and that, therefore, the proportion of plasma filtered (filtration fraction) will vary with the intracapillary pressure. The pressure within the glomerular capillaries can and does vary, depending upon the relative tonus of the afferent and efferent arterioles.

Let us assume that only one set of vessels change tonus at a time:

1. Constriction of the afferent arterioles (leading into the glomerulus) would: (a) diminish the renal plasma flow (diodrast clearance); (b) decrease the pressure distal to the constriction, in the glomerular capillaries, and the filtration would fall markedly; (c) decrease the filtration fraction because the filtration falls more, relatively, than does the plasma flow.

2. Constriction of the glomerular capillaries would: (a) diminish the renal plasma flow; (b) decrease the filtration; (c) not affect greatly the filtration fraction, because the intracapillary pressure is not much changed.

3. Constriction of the efferent arterioles would: (a) diminish the renal plasma flow; (b) increase the intravascular pressure proximal to the constriction, in the glomerular capillaries, and thus increase the filtration fraction; (c) maintain a normal filtration volume in the face of a deficit in plasma flow. (Smith and others[20] have demonstrated mathematically that filtration will remain constant when the volume of plasma flow is regulated by the tonus of the efferent arterioles, *i.e.*, the filtration fraction will vary inversely as the plasma flow.)

Thus we see that the "male type" of essential hypertension is associated with constriction of the efferent arterioles. This explains why most clinical tests of renal function remain normal in uncomplicated essential hypertension, even though the renal plasma (and whole blood) flow may be reduced by as much as 50 per cent.

We have measured the renal plasma flow in 15 women with hypertension following toxemia of pregnancy, and in 7 posttoxemic women with normal blood pressures. Simultaneously we have determined the urea clearances, and made a rough estimate of the glomerular filtration therefrom. The data in Table II indicate that the filtration fraction is normal in all but 2 cases, though considerable decreases are usually found in the renal plasma flows. This is in marked contrast to the findings in the "male type" of hypertension.

In posttoxemic hypertension, we find: (a) diminished plasma flow (usually), (b) diminished filtration (usually), and (c) normal filtration fraction. These findings point to the glomerular capillaries as the site of obstruction to the blood flow. Either there are fewer glomeruli than normal, or the lumina of the capillaries are narrowed. It is just such capillary narrowing which Bell,[12] and Page and Cox[14] have described as persisting after toxemia of pregnancy. If these glomerular

TABLE II. RENAL HEMODYNAMICS IN POSTTOXEMIC HYPERTENSIVE WOMEN

AGE YEARS	POST PARTUM YEARS	BLOOD PRESSURE MM. HG	PLASMA CLEARANCE OF		CALCULATED GLOMERULAR FILTRATION ML. PER MINUTE	FILTRATION FRACTION PER CENT	DEFICIT IN RENAL BLOOD FLOW* PER CENT
			DIODRAST ML. PER MINUTE	UREA ML. PER MINUTE			
41	0.1	170/106	358	68.0	113.3	31.6	41
30	1.3	192/120	434	48.1	80.1	18.5	18
34	3.2	152/90	403	52.0	86.7	21.5	30
37	3.4	180/130	538	58.4	97.3	18.1	2
48	4.7	168/90	430	43.2	72.0	16.8	10
37	2.2	170/120	437	70.2	116.9	26.8	17
48	3.6	150/90	517	62.2	103.6	20.0	4
38	5.5	210/140	376	38.3	63.8	17.0	33
40	2.0	240/126	450	57.9	96.5	21.5	24
39	1.8	220/120	377	40.5	67.5	17.9	30
48	5.0	220/110	382	38.6	64.4	16.8	31
40	4.0	190/150	349	47.5	79.2	22.7	40
30	0.6	180/120	454	53.2	88.8	19.5	19
24	0.1	170/100	531	63.0	105.0	19.8	10
35	1.3	140/90	392	54.9	91.6	23.3	28

*As compared with average normal of 850 ml. per minute.

lesions do persist, they serve to explain the renal blood flows and filtration fractions which we have observed. Since the thickening of the basement membranes of the glomerular capillaries is thought to be specific for toxemia of pregnancy, it would follow that the renal ischemia found at follow-up is a consequence of the toxemia.

There are two possible alternative explanations for the observed relationships between the plasma flows and filtration volumes. (a) Both afferent and efferent arterioles may be constricted, the increased tonus being so balanced as to maintain a normal filtration fraction at the expense of the filtration volume. (b) Since the glomerular filtration is estimated from the maximal urea clearance, an unusually great back-diffusion of urea from the tubules could account for an *apparent* reduction in filtration volume. This increased back-diffusion of urea would then have to be exactly balanced with the renal blood flow so as to main-

tain an *apparently* normal filtration fraction as estimated from the urea clearance, although the actual filtration fraction were elevated. Neither of these alternatives appeals to us so much as does the first explanation, which incriminates the capillaries.

Whether the posttoxemic hypertension is *caused* by the disturbance in renal hemodynamics cannot be finally decided at the present time. It seems logical to suppose that the narrowing of the capillary lumina might lead to hypertension. The probable mechanism of renal hypertension, as simplified from the publications of Page[8] might be summarized as follows:

1. Reduction in intrarenal pulse pressure (lessened difference between systolic and diastolic pressures *in the kidney*).
2. Release of renin from the kidney.
3. Activation of renin → angiotonin (the pressor substance).
4. Generalized arteriolar constriction, *especially marked in efferent glomerular arterioles.*
5. Further reduction in the intrarenal pulse pressure (because of 4), thus establishing a vicious cycle which maintains hypertension.

Reduction in the lumina of the glomerular capillaries would, of course, offer an increased resistance to perfusion. This would result in an increased back-pressure, and thus the intrarenal diastolic pressure would be increased. The systolic pressure remaining constant, the intrarenal pulse pressure must be diminished. Such reduction in pulse pressure appears to be the stimulus for the release of renin from the kidney.

Posttoxemic hypertension seems not to fulfill one of the postulates (Number 4 in the above summary) in that the efferent arterioles do not *appear* to be constricted. If they really are not constricted, then this form of hypertension is not a typical renal hypertension. However, the efferent arterioles may be constricted, and the expected increase in filtration fraction not found because of diminished capillary permeability. We do not know whether the thickened basement membrane, if present, would be less permeable than normal. If its permeability were diminished, then the constriction of the efferent arterioles would be masked, since the increased intraglomerular pressure would be expended in maintaining a normal filtration fraction.

TABLE III. RENAL HEMODYNAMICS IN POSTTOXEMIC WOMEN WITH NORMAL BLOOD PRESSURES

AGE YEARS	POST PARTUM YEARS	BLOOD PRESSURE MM. HG	PLASMA CLEARANCE OF		CALCULATED GLOMERULAR FILTRATION ML./MIN.	FILTRATION FRACTION PER CENT	DEFICIT IN RENAL BLOOD FLOW PER CENT
			DIODRAST ML./MIN.	UREA ML./MIN.			
23	1.0	90/50	637	65.6	109	17.1	(−13)*
38	4.2	110/66	411	55.0	92	22.2	28
36	1.1	98/60	721	98.0	163	22.5	(−13)*
32	3.5	100/70	435	36.0	60	13.8	25
25	1.5	110/70	493	60.9	101	20.5	18
18	1.8	114/74	459	35.9	60	13.1	14
35	1.3	120/70	392	54.9	92	23.3	28

*Renal blood flow 13 per cent above average normal of 850 ml. per minute.

Having demonstrated that there is usually some reduction in the renal blood flow in posttoxemic hypertension, we were interested to know what might be found in posttoxemic women with normal blood pressures. In Table III are summarized the measurements made in 7 women, all of whom had had either eclampsia or severe preeclampsia within the past 1 to 4.2 years. In several of these cases the deficit in renal blood flow, as compared with average normal, is greater than that found in some of the hypertensives. In 2 cases, the filtration fractions are very low (possibly because of decreased glomerular permeability?). While none of these women is hypertensive, some degree of renal damage may be present in 5 of the 7. Perhaps hypertension itself prevents the appearance of more marked renal ischemia in the patients with high blood pressure; this has been more fully discussed elsewhere (Chesley and Chesley[19]).

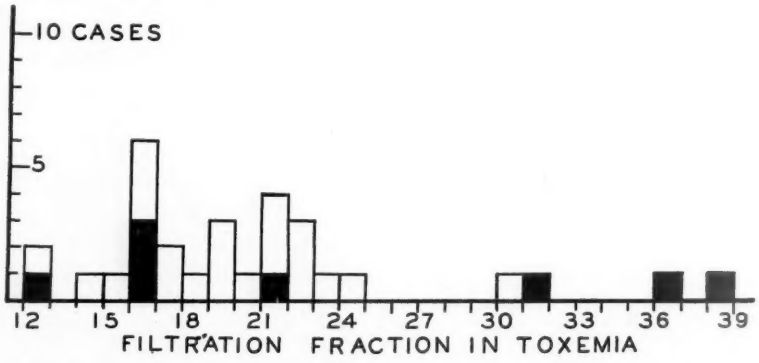

Chart 1.—The relation between the filtration fraction as measured at the height of toxemia and the presence or absence of hypertension (above 140/90) two years later. Black squares represent hypertensives; white squares represent patients with normal blood pressure.

RELATION OF THE FILTRATION FRACTION IN TOXEMIA TO SUBSEQUENT HYPERTENSION

We[21] have measured the renal blood flow during the acute phase of toxemia, and found that it is characteristically normal, although there is a wider range above and below average than we[22] found in normal women. In these toxemic women the filtration fractions vary widely, and many values are definitely abnormal. Fig. 1 shows the distribution of the filtration fractions as determined at the height of the acute toxemia. (Our findings as regards renal blood flow and filtration fractions in toxemia have recently been confirmed by Corcoran and Page,[23] and by Taylor[24].)

We have re-examined all of our patients at twenty to twenty-four months after the measurement of renal function, and find a correlation between the filtration fraction as then determined and the blood pressure of today.

Following the argument outlined above, these patients may be divided into 3 groups on the basis of their filtration fractions during toxemia.

Group A. Patients With High Filtration Fractions (Above 25 Per Cent).—Women in this group exhibit the efferent arteriolar constriction characteristic of the "male type" of hypertension. Four such cases were observed (2 unpublished). Of these, 3 were known to have had hypertension antedating the first pregnancy, and now have elevated blood pressure at two years after delivery. In the fourth case, the pre-eclampsia was complicated by pyelitis which may have disturbed the renal hemodynamics; this patient is now normal.

Group B. Patients With Low Filtration Fractions (Below 17 Per Cent).—In the 10 patients showing lowered filtration fractions, it is presumed that glomerular

capillary damage is responsible for the disproportionate fall in glomerular filtration. Women showing such decreased filtration fractions in toxemia of pregnancy, therefore, have sustained more severe glomerular damage than have the patients having normal filtration fractions. *If toxemia of pregnancy causes subsequent hypertension, these women with low filtration fractions should show a high incidence of later hypertension.* As Fig. 1 indicates, 4 patients of 10 do have hypertension at follow-up. Whether the other 6 will eventually have hypertension, or be more susceptible to recurrence of toxemia we cannot yet say.

Group C. Patients With Normal Filtration Fractions (17 to 25 Per Cent).—In the 16 patients having normal filtration fractions during toxemia, glomerular damage might be considered as slight. At follow-up, only 1 of these patients was found to have hypertension, and she has had repeated toxemia.

In brief: of 16 patients having normal filtration fractions during toxemia of pregnancy, only 1, 6.3 per cent, is now hypertensive. Of 14 patients showing abnormal filtration fractions during toxemia, 7 or 50 per cent, are now hypertensive.

COMMENT

Regardless of the interpretations, admittedly speculative, the objective observation remains that laboratory methods will differentiate between posttoxemic and the "male type" of cardiovascular hypertension. While there are alternative possibilities, the findings are most plausibly explained on the basis of residual damage left by the toxemia, as described by Bell: "It may be said, therefore, that chronic renal disease may result from the acute lesion of eclampsia, but it is a special type differing from the known forms of chronic renal disease in its structure and pathogenesis. On the basis of the anatomical structure, one would expect to find hypertension and renal insufficiency clinically."

I desire to acknowledge my indebtedness to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters who have read and criticized the typescript of this paper.

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THE EFFECTS OF CERTAIN GONADOTROPIC EXTRACTS ON ANOVULATORY CYCLES AND AMENORRHEA

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ABNORMAL physiology of endocrine glands has become increasingly recognized in the past few years as an occasional cause of sterility in both the male and the female.

This abnormality may manifest itself in the female by anovulatory cycles which may not be recognizable by menstrual phenomena from normal ovulatory cycles.

The delicate interrelationship of the pituitary and ovary in producing endometrial changes and controlling menstruation and the apparent control of the pituitary over ovulation have led to the conclusion that the causative factor in at least certain cases of anovulation may be deficient pituitary activity. Therefore attempts are being made to stimulate ovulation in the anovulatory patient with various gonadotropic products.

Davis and Koff[1] first reported success in stimulating ovulation with the gonadotropic factor of pregnant mares serum in 1938 and later Siegler and Fein[2] duplicated their findings in a higher percentage of cases. None of the patients, however, were proved to be previously anovulatory. In other words, ovulation was observed in an ovary which might have been normally ovulating even without gonadotropic treatment.

On the other hand, Gray,[3] in a carefully controlled series of patients with abnormal menstruation and shown to be anovulatory, found some evidence of correction of irregularities, especially in amenorrhea, and occasional development of secretory endometrium following pregnant mares serum therapy.

Huber and Davis,[4] working with anovulatory patients, also produced secretory activity in some cases following pregnant mares serum administration and pregnancies occurred in a few instances.

Hartman,[5] using the *Macacus rhesus,* an animal which in captivity is physiologically anovulatory during certain months of the year and frequently anovulatory at other times, found that ovulation was *probably* induced in a small proportion (7 in 104) of animals injected with pregnant mares serum.

It is difficult to judge how frequently anovulatory menstruation occurs in the human being. This phenomenon was mentioned by Gardner[6] as early as 1856 as a possible cause for sterility in women. Rock, Bartlett and Matson[7] found 36 patients in a series of 392 who showed evidence of anovulation; Novak[8] found 39 in 142 cases, while Israel and Mazer[9] noticed 36 in 109.

Repeated biopsies and pregnanediol determinations on 83 sterility cases from a clinic in the Sloane Hospital for Women disclosed 7 patients who were consistently anovulatory and 2 others who had occasional anovulatory cycles. The menstrual cycles in some of these cases were irregular, but similar irregularity also occurred in patients who regularly developed secretory endometrium.

If the above figures are taken as a group, the percentage of anovulation in women complaining of sterility is about 16. It would be incorrect to conclude, however, that 16 per cent of sterility is caused by anovulation, as many of the above cases doubtless have other sterility stigmas, but at the same time the percentage is high enough to demand consideration of anovulation as a significant sterility factor.

Any investigation concerning the problem of ovulation obviously requires accurate methods for the diagnosis of this phenomenon. Since it is generally supposed that the formation of a corpus luteum occurs only after ovulation, and since it is possible to obtain evidence of luteal secretion, the most accurate diagnosis of ovulation at the present time rests largely on the evidence of activity of the corpus luteum. This evidence is obtainable not only from the endometrium by biopsy, but also from the urinary excretion of pregnanediol. This substance, shown by Venning[10] to be an excretion product of the corpus luteum hormone, progesterone, is susceptible to quantitative chemical identification. Therefore, it seems justifiable to assume that ovulation has occurred if either one, or better both, of these tests are positive, although there could be a rare exception due to imprisonment of the ovum in the ruptured follicle.

MATERIAL

Ten patients (7 from the clinic of the Sloane Hospital for Women, 3 from private practice), who were judged to be anovulatory by the above methods of diagnosis, were treated with various quantities and types of gonadotropic extracts. In most cases pregnant mares serum extract (Gonadin, Cutter) and in a few cases pregnancy urine extract plus whole pituitary synergist (Synapoidin, Parke Davis & Co.) were used. In all cases these patients had the conventional sterility investigation, consisting of history, physical examination, urinalysis, blood count, Wassermann, basal metabolic rate, blood cholesterol, Rubin test, examination of husband, etc. Abnormalities other than anovulation are noted if present.

Pregnant mares serum or the synergist product was administered for the most part during the first two weeks of the menstrual cycle, usually in four dosages of 1 c.c. each (200 Cole-Saunders units of pregnant mares serum per c.c.), although there were occasional variations which will be mentioned in specific instances. Huber and Davis[4] injected intramuscularly 20 Cortland-Nelson units (equal to 200 Cole-Saunders units) of pregnant mares serum on each day from the seventh to tenth days and 60 units intravenously on the eleventh day. Gray[3] favored a similar technique using somewhat smaller dosages.

RESULTS

Four cases showed evidence of ovulation following prolonged administration of gonadin (Fig. 1). It will be observed that the gonadin dosage varied somewhat in the different menstrual cycles and that the cycles themselves were quite irregular. When evidence of ovulation was observed following therapy, it was noted that, in every case but one (Case 5), treatment had been started during menstruation and stopped at about the theoretical time of ovulation. Although this may be of no significance, it is remarked upon because the time relationship between the menstrual cycle and the date of administration has been considered extremely important.

The patients in Cases 5 and 7 in our series (Fig. 1) had been subjected to previous gynecologic operations elsewhere, involving, in the first case, unilateral oophorectomy, and in the second unilateral oophorectomy and partial resection of the other ovary. In these latter two cases no, or practically no, pregnanediol was present, even though secretory endometrium was found. In Case 5 this was because the specimens were collected the day before the onset of menstruation, when pregnanediol is

usually absent, and in Case 7 it may possibly be due to the fact that there are occasional twenty-four-hour lapses even in normal excretion.[11]

In the above cases, evidence of ovulation occurred occasionally following gonadotropic therapy. It is a question whether or not this therapy has actually caused the subsequent ovulation either in these

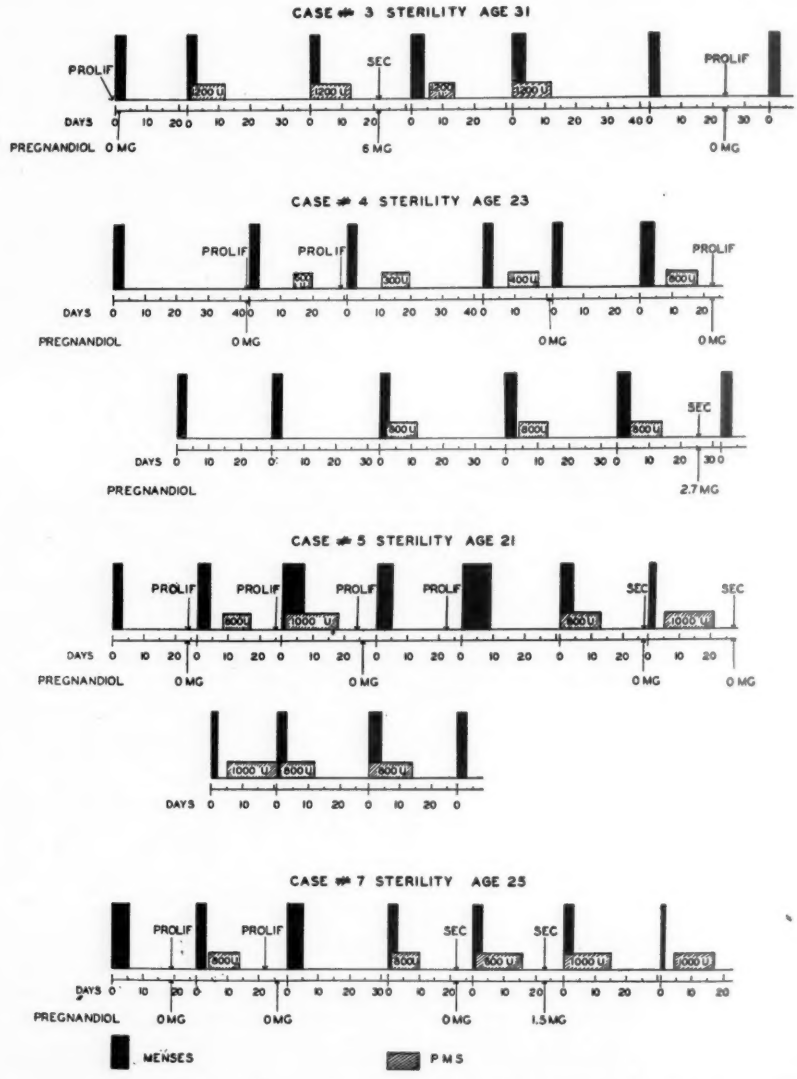

Fig. 1.—Four cases showing evidence of ovulation during courses of pregnant mares serum administration. Arrows pointing downward represent endometrial biopsy with diagnosis of proliferative or secretory endometrium as indicated.

cases or similar ones reported elsewhere in the literature. It is a well-known fact that many untreated women ovulate sporadically even though menstruating regularly,[7, 8, 12] just as the above treated patients

have done. Fig. 2 describes two patients of this type. The patient in Case 8 received thyroid therapy throughout the period of investigation, a fact which might conceivably explain the second ovulatory period but not the first.

Therefore, in patients previously treated with pregnant mares serum, we can by no means be certain that ovulation was a result of this treatment, for it might have occurred without treatment.

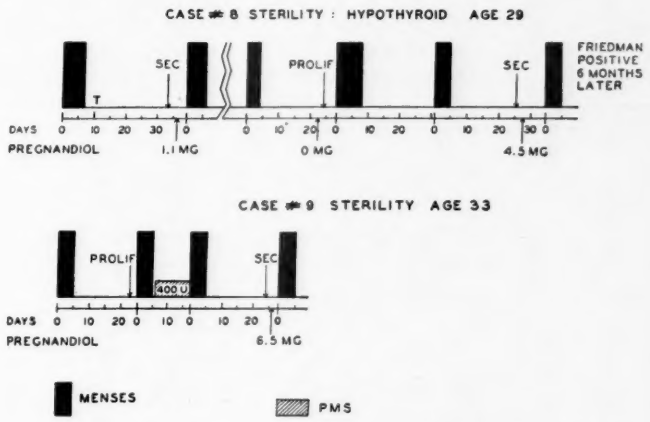
CASE # 8 STERILITY : HYPOTHYROID AGE 29
SEC
PROLIF
SEC
FRIEDMAN POSITIVE 6 MONTHS LATER
T
DAYS 0 10 20 30 0 0 10 20 0 10 20 0 10 20 30 0
PREGNANDIOL 1.1 MG 0 MG 4.5 MG
CASE # 9 STERILITY AGE 33
PROLIF
400 U
SEC
DAYS 0 10 20 0 10 0 10 20 0
PREGNANDIOL 6.5 MG
MENSES
PMS

Fig. 2.—Two cases showing evidence of occasional ovulation without treatment. Arrows pointing downward represent endometrial biopsy with diagnosis of proliferative or secretory endometrium as indicated. "*T*" in Case 8 represents the beginning of thyroid therapy.

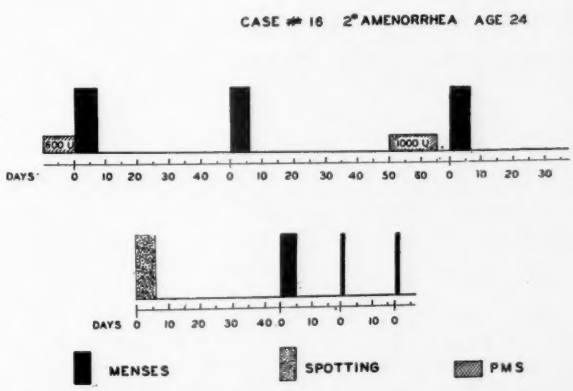

Fig. 3.—One patient with amenorrhea of eight months who had irregular periods of bleeding following pregnant mares serum therapy.

In addition to the use of the gonadotropic factor on the anovulatory patient, this substance was administered to patients complaining of secondary amenorrhea. These patients were also sterile but without other demonstrable abnormalities. Cases of amenorrhea in the absence of other symptoms have not been treated unless pregnancy is desired. Two patients of 10 treated are thought to have shown a possible reaction to therapy.

One of these (Case 16, Fig. 3) menstruated irregularly for a year (and possibly longer) following treatment, whereas previously she had suffered from amenorrhea for eight months. She did not conceive, however, and her peroids of bleeding were totally irregular.

The other patients thought to have reacted to gonadotropic stimulation presented an interesting phenomenon diagnosed as primary pituitary failure due to an unknown cause at the age of 31 years. She complained of oligomenorrhea, menstruating about three times a year, headaches, severe hot flushes, 36 pounds' gain in weight in one year, polydypsia and polyuria and a four-year history of sterility. Treatment and complete laboratory workup were negative. Urine extraction for follicle-stimulating hormone showed none to be present (contrary to the picture seen in menopausal urine); x-ray of the sella turcica showed no abnormalities and repeated basal metabolism rate determinations were normal.

She received 7 c.c. of pregnancy urine plus pituitary synergist over a period of twenty-six days, and pregnancy was evident about six weeks following the first injection. She later delivered uniovular twins.

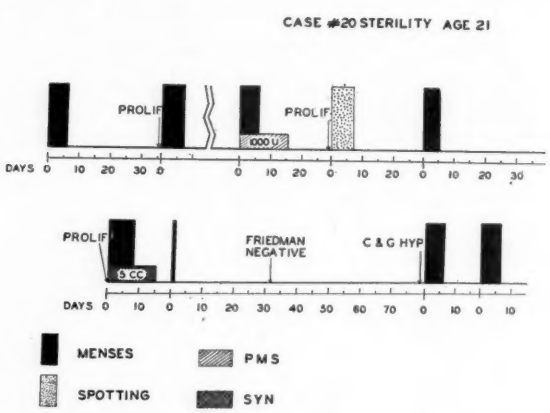

Fig. 4.—One patient who developed amenorrhea and ovarian cyst formation following gonadotropic therapy. Proliferative and cystic-glandular hyperplastic endometriums are diagnoses of tissue obtained by biopsy.

None of the other amenorrheic cases was benefited in the slightest by the treatment even after bleeding had been stimulated by estrogens.

Possible harmful effects of gonadotropic stimulation of the ovary may occur. Smith, Kurzrok and Watson[13] demonstrated ovarian cyst formation following large dosage of pregnant mares serum, and Hartman[5] has observed this phenomenon in the monkey. Case 20 (Fig. 4) developed amenorrhea following pregnancy urine-synergist treatment in conjunction with a gradually enlarging adnexal mass thought to be an ovarian cyst. Subsequent biopsy disclosed cystic glandular hyperplasia of the endometrium and following a period of bleeding the adnexal mass disappeared. It was thought that in this case stimulation of estrogen production was so great that bleeding was prevented by excessive estrogen secretion and that ultimately bleeding resulted as an estrogen withdrawal phenomenon.

The significance of antihormone development following pregnant mares serum administration is as yet unknown. Meyer and Wolfe[14] observed antigonadotropic activity following injection of even small amounts of pregnant mares serum in the monkey, and this phenomenon was found by Jailer and Leathem[15] to occur also in the human being. There is as yet no evidence to show that this antihormone production is inhibitory to the patient's own gonadotropins.

SUMMARY

Sterile patients with either anovulatory menstruation or amenorrhea were treated with the gonadotropic extracts from pregnant mares serum

(gonadin, Cutter) or pregnancy urine plus pituitary synergist (synapoidin, Parke Davis & Co.).

CONCLUSIONS

1. Ovulation may have been caused in 4 previously anovulatory cases by pregnant mares serum, although this is not conclusive because other previously anovulatory cases were observed who ovulated without treatment. There were no pregnancies following the use of pregnant mares serum.

2. One patient complaining of amenorrhea for eight months menstruated irregularly for at least one year following pregnant mares serum treatment.

3. One patient diagnosed as having primary pituitary insufficiency became pregnant following pregnancy urine-pituitary synergist treatment. This is the only pregnancy in this series.

4. Possible harmful effects of gonadotropic stimulation, such as ovarian cyst formation and antihormone production, may occur. One patient treated with pregnancy urine-pituitary synergist developed amenorrhea and an ovarian cyst. Menstruation occurred and the cyst regressed following cessation of treatment.

It is impossible at this time to say whether or not the above evidences of ovulation are due to coincidence or to the results of treatment. Certainly the time sequence in the "successful" cases indicates a cause and effect relationship. It must be remembered that these cases were "successful" only so far as evidence of corpus luteum activity occurred. No pregnancies resulted in the patients receiving pregnant mares serum treatment.

The evidence for the induction of ovulation by pregnant mares serum or pregnancy urine-pituitary synergist is therefore suggestive but by no means conclusive.

The gonadotropic substances used were pregnant mares serum extract (Gonadin, Cutter) and pregnancy urine extract plus whole pituitary synergist (Synapoidin, Parke, Davis & Co.). These substances were supplied through the courtesy of Dr. Donald H. Wonder of Cutter Laboratories and of Dr. E. A. Sharp of Parke, Davis & Company.

I wish to express my gratitude to Dr. B. P. Watson, Director of the Sloane Hospital for Women, and to Dr. Earl T. Engle, Professor of Anatomy, Columbia University, College of Physicians and Surgeons, for their helpful advice and suggestions during the course of this study.

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ARE ESTROGENS CARCINOGENIC IN THE HUMAN FEMALE?

II. Atypical Endometrial Proliferation in a Patient Treated With Estrogens

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SINCE the widespread use of estrogens in recent years, the relationship of estrogens to carcinogenesis, has become a problem of great importance to the clinician. The original report of Lacassagne,[1] of the production of mammary carcinoma in male mice bred from female mice with a high incidence of spontaneous mammary carcinoma, has been amply confirmed.[2] Loeb[3] concluded that both genetic and hormonal factors have important roles in the production of mammary carcinoma. This conclusion is supported by the fact that mammary carcinoma has thus far been produced by estrogens only in inbred male mice from "high tumor" strains. Metaplasia of the epithelium of the cervix has been produced following the administration of estrogens plus trauma in monkeys[4] and guinea pigs.[5] In mice, Gardner, Allen, and Smith[6] have reported carcinomatous lesions of the cervix following estrogen injections. In the human being, Allasen and Owen,[7] and Auchincloss and Haagensen[8] have reported the occurrence of adenocarcinoma of the breast in patients treated with estrogens. On the other hand, we could find no evidence of abnormal proliferation in the endometrial or vaginal mucosa[9] in a series of 206 patients who had been treated with huge doses of estrogens over periods of time extending to five and one-half years.

The possibility of estrogens having carcinogenic potency in human beings is fraught with such serious implications that all cases, in which there appears to be some such relationship, should be investigated very thoroughly. Here we wish to report a case which illustrates this problem.

CASE REPORT

The patient was a 52-year-old, gravida iii, para ii, who was admitted to the Gynecological Clinic of the Mount Sinai Hospital, in June, 1938, complaining of menopausal symptoms of two years' duration. Her last menses had occurred two years prior to admission. The past history was irrelevant. The available family history revealed no predisposition or tendency to carcinoma. The father had died of a strangulated hernia at the age of 53. The mother had died at the age of 70. The cause of death was unknown. One brother and sister are alive and well. The patient's husband had died of cancer of the stomach. Pelvic examination revealed a parous introitus; the vagina was uninflamed. The cervix was lacerated and the uterus was slightly enlarged by the presence of small fibroids. The adnexa were not palpable. From June 20, 1938, to Aug. 5, 1938, the patient received 40,000 R.U. of α-estradiol benzoate. There was no immediate withdrawal bleeding. Several months later, on Dec. 21, 1938, spontaneous uterine bleeding occurred. Examination revealed a small cervical polyp which was removed. The endometrium, obtained at

the same time by suction curettage, showed a variable picture with areas of moderate proliferation interspersed with areas of hypoplasia.

Because of a recurrence of the menopausal symptoms, estrogen therapy was resumed in January, 1939. From Jan. 4 to Feb. 7, 1939, this patient received 234,000 R.U. of α-estradiol benzoate, administered intramuscularly, in addition to

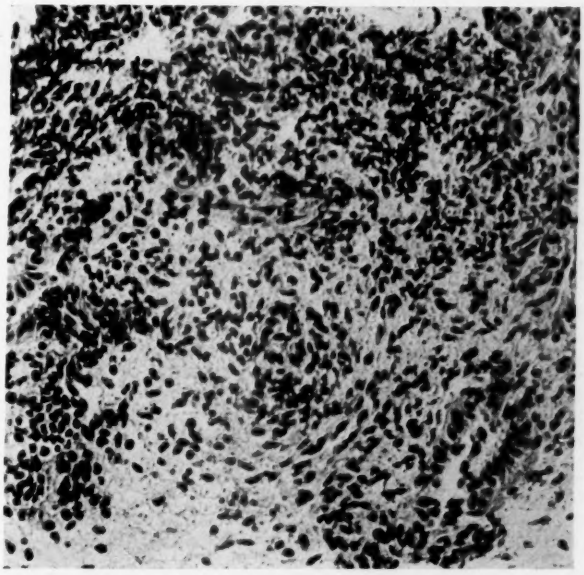

Fig. 1.—Endometrial biopsy (No. 69072—March 20, 1939). Note advanced atrophy; only 3 small shrunken glands surrounded by an inactive stroma. (×285.)

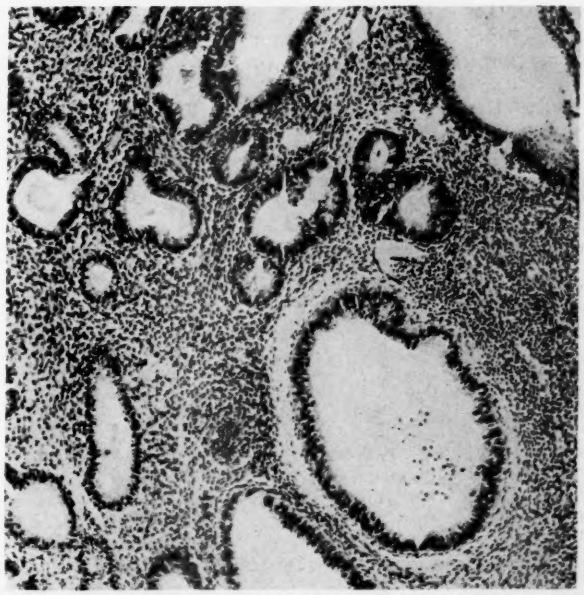

Fig. 2.—Endometrial biopsy (No. 71098—June 17, 1940), approximately three months after implantation. Note persistent estrogenic effect; numerous proliferating glands with several large, dilated glands, consistent with diagnosis of slight hyperplasia. (×103.)

65 mg. of progesterone. The latter hormone was given in divided doses during the last ten days of this course of injections. Prior to the administration of the progesterone, an endometrial biopsy revealed an advanced proliferative endometrium with areas of cystic hyperplasia. Following the administration of the progesterone, the endometrium revealed a mixed picture of proliferative and advanced secretory

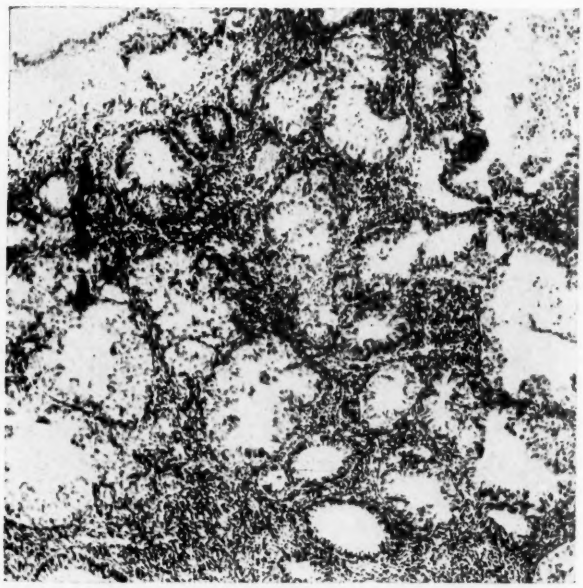

Fig. 3, *A*.—Endometrial biopsy (No. 72063—Sept. 9, 1940), approximately five and one-half months postimplantation. Note numerous glands with stratification and budding. Some glands contain leucocytes and desquamated epithelial cells. (×105.)

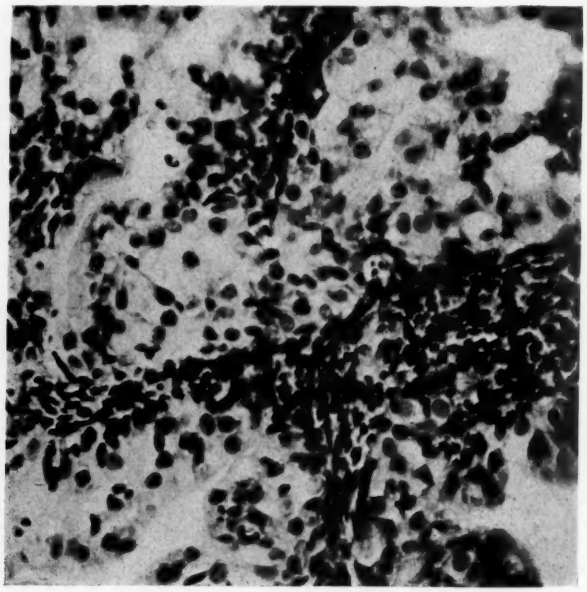

Fig. 3, *B*.—Higher power magnification of Fig. 3, A. (×425.)

phenomena. The patient received no treatment for approximately six months and, on June 20, 1939, a single pellet of crystalline *a*-estradiol (25 mg.) was implanted subcutaneously in the right thigh because of the return of severe evidence of estrogen deficiency. The patient was apparently relieved of her symptoms and did not return to the follow-up clinic until seven months later. At this time, she complained of a recurrence of menopausal symptoms. On March 20, 1940, approximately nine

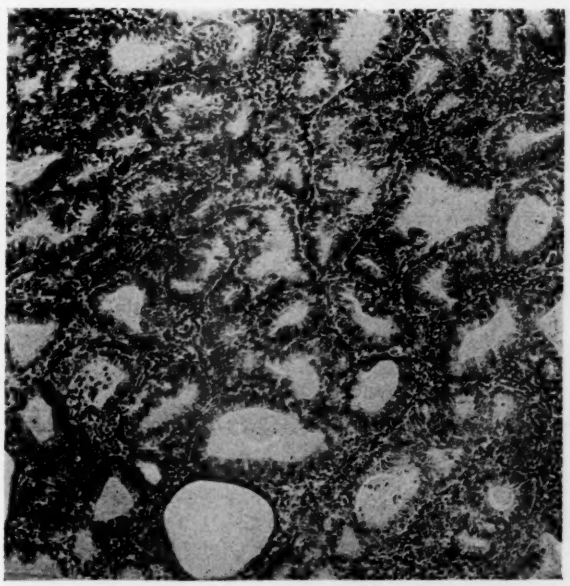

Fig. 4, *A*.—Endometrial biopsy (No. 72426—Oct. 8, 1940), approximately six and one-half months postimplantation. (×110.)

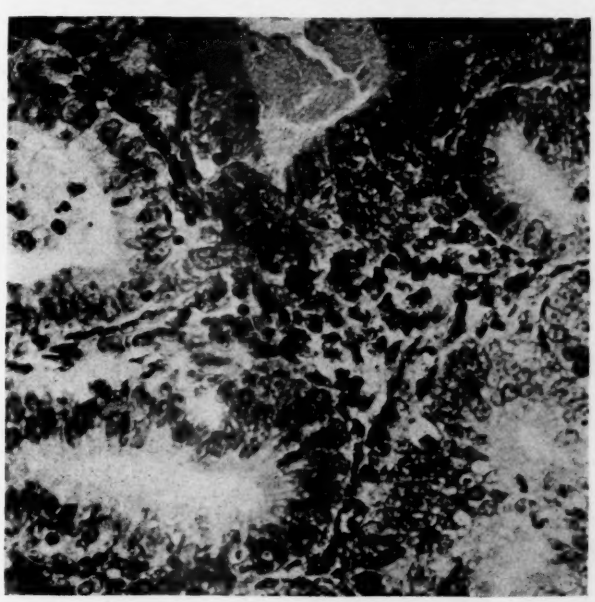

Fig. 4, *B*.—Higher power magnification of Fig. 4, *A*. Note increased number of mitotic figures; close approximation of glands with diminished intervening stroma; epithelial stratification. (×425.)

months after the implantation of the α-estradiol pellet, the implantation site was excised.[10] Endometrial and vaginal biopsies were taken at the time of excision and revealed morphologic regression to the pre-implant status, viz., atrophy of the endometrium (Fig. 1) and evidence of estrogen deficiency in the vaginal biopsy. At this time, the patient was re-implanted with 29 mg. of loose crystals of α-estradiol benzoate. Six weeks after this implantation, moderate uterine bleeding occurred and intermittent spotting persisted for approximately six weeks. At the end of this time (June 17, 1940), an endometrial biopsy showed advanced proliferation with numerous dilated glands (Fig. 2). Five days after the suction curettage, the bleeding stopped, only to recur on Sept. 9, 1940. At this time, another endometrial biopsy was obtained by suction curettage and revealed a variable endometrial pattern. In some areas, the endometrial glands and stroma were atrophic, whereas, in other areas, there was evidence of moderate proliferative activity with several dilated, cystic glands. In addition, one small fragment of endometrium revealed several closely packed glands which were lined by large, pale, epithelial

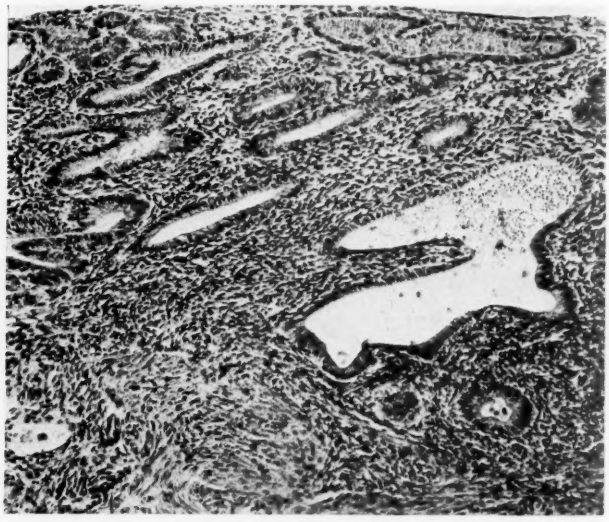

Fig. 5.—Endometrium of extirpated uterus (No. 72509—Oct. 17, 1940) showing moderate proliferation and a few dilated cystic glands. Note no evidence of neoplastic change. (×103.)

cells with ovoid nuclei and increased amounts of cystoplasm containing large vacuoles. These cells showed marked pseudostratification and in some glands the entire lumen was obliterated by sheets of cells (Figs. 3, *A* and *B*).

Up to this time, the patient had had 7 endometrial and vaginal biopsies and in no instance had there been any evidence of abnormal cellular proliferation or atypism. Following the last suction curettage, slight uterine bleeding continued. It is pertinent to note here that, although we have often noted uterine bleeding following implantation of estrogens, the bleeding is usually of short duration and frequently stops immediately after a suction curettage. In view of the abnormal type of bleeding and the atypical glandular changes noted in the endometrium, a diagnostic curettage, under anesthesia, was performed on Oct. 8, 1940, approximately one month after the last suction curettage.

Following microscopic examination of the curettings, a diagnosis of adenocarcinoma of the uterus was made by Dr. Paul Klemperer, pathologist at the Mount Sinai Hospital. This opinion was based on "the fact that the glands are very closely approximated with very little intervening stroma; that the epithelial cells show stratification and many mitotic figures" (Figs. 4, *A* and *B*).

On Oct. 16, 1940, a hysterectomy was performed. The uterus was normal in size and contained 2 small myomas and a small endometrial polyp. Several strips of endometrium were examined histologically and showed no evidence of carcinoma, metaplasia, or cellular atypism (Fig. 5).

DISCUSSION

As noted above, the extirpated uterus did not reveal any evidence of adenocarcinoma. The question arises as to the validity of the diagnosis of adenocarcinoma in the endometrial biopsies obtained prior to hysterectomy. After careful histologic study and re-evaluation of the clinical course, we believe that we were dealing with an atypical, but benign, endometrial lesion. This opinion is based upon the following: (a) The gland patterns showed only slight variation from normal. (b) There was no evidence of invasion of the stroma. (c) Pseudostratification and an increased number of mitotic figures occur normally in the proliferative phase of the menstrual cycle, as well as in endometriums stimulated by exogenous estrogens. (d) The gland pattern showed a relatively uniform regular appearance with an absence of "lawlessness" of tissue growth, which is associated with carcinoma.

However, it cannot be denied that the pathologic picture encountered is one which would immediately make the pathologist suspect carcinoma. It is apparent that the borderline histologic characteristics of the lesion permits of dual interpretation and, therefore, it was felt advisable to have some other opinions. Accordingly, the microscopic sections were sent to Dr. Robert Meyer, of the University of Wisconsin, Dr. Emil Novak, of Johns Hopkins University, and Dr. Herbert Traut, of Cornell University. Drs. Meyer and Novak were of the opinion that the lesion was benign. Dr. Traut was in agreement with Drs. Paul Klemperer and Sadao Otani, of the Mount Sinai Hospital, and considered the lesion to represent an early adenocarcinoma of the endometrium. Evidently, judged by histologic criteria alone, the question of the neoplastic character of the lesion cannot be categorically answered.

Another question which remains to be answered is the relationship of the administered estrogens to the endometrial lesion. Can we assign to estrogens an etiologic role in this case? We believe that the question should be answered in the negative for the following reasons: First, the localization of the atypical endometrial pattern to such a small area of endometrium makes it unlikely that the atypism was due to so general a stimulating agent as estrogens. If the opposite were true, we might expect multiple foci of abnormal change. Second, endometrial patterns, as described in this case, have been reported by Novak[11] as occurring spontaneously in postmenopausal women. These patients have been observed for several years and have not developed carcinoma of the uterus.[12]

In conclusion, it is suggested that extreme caution be used before attributing carcinogenic properties to estrogens in human beings, lest an extremely valuable therapeutic agent be condemned unjustly.

For the estrogens used in this investigation, we are indebted to Dr. Erwin Schwenk, of the Schering Corporation, Bloomfield, N. J.

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CERVICAL DYSTOCIA*

A STUDY OF EIGHTY-SIX CASES

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IN CONSIDERING abnormal labor most textbooks devote little space to cervical dystocia and many authorities question its existence. The failure of prompt cervical dilatation is attributed either to cephalopelvic disproportion, to abnormal presentation, position, or attitude of the fetus, or to uterine inertia as a consequence of prematurity, toxemia, endocrine or medical infirmities. Yet a subsequent labor may be rapid and easy despite repetition of the same circumstances.

The following report is an attempt to determine the true frequency of cervical dystocia together with an analysis of the possible causative factors, clinical course, treatment, and end-results. For this study cervical dystocia is defined as difficult labor due principally to failure of the cervix to dilate and to be effaced within reasonable time despite frequent and forceful uterine contractions. Implied in this definition is the absence of those common causes of dystocia noted in the preceding paragraph.

MATERIAL

Among 8,213 confinements at the Woman's Hospital during the six years 1930 to 1935 inclusive, only 86 cases satisfied the above criteria, an incidence of 1.05 per cent (Table I). Of 382 prolonged labors, thirty-six hours or more, cervical dystocia was the major cause in 51 cases, or 13.4 per cent. On critical re-study it was accepted as the major indication for 45 out of 474 cesarean sections (9.5 per cent), 2 out of 34 high forceps (5.9 per cent), 28 out of 778 medium forceps (3.6 per cent), and 9 out of 591 low forceps operations (1.7 per cent).

Many other "cervical dystocia" histories were excluded because the evidence was insufficient to rule out disproportion, malposition, or inertia. On the other hand some cases of transverse and posterior oc-

*Read, by invitation, at a meeting of the Richmond Academy of Medicine, Richmond, Virginia, November 12, 1940.

TABLE I. INCIDENCE OF CERVICAL DYSTOCIA DURING SIX YEARS 1930-1935 INCLUSIVE

	TOTAL CASES	CERVICAL DYSTOCIA	
		CASES	PERCENTAGE
Viable confinements	8,213	86	1.05
Prolonged labors	382	51	13.4
Cesarean sections	474	45	9.5
High forceps	34	2	5.9
Medium forceps	778	28	3.6
Low forceps excluding prophylactic	591	9	1.7

ciput were included, for instance when subsequent delivery of an equally large baby was rapid and easy despite repetition of the malposition. Certain history charts were accepted only after discussion with the responsible surgeon. But with due allowance for a large personal element in judging each case, the above figures indicate trouble with the cervix as the major factor in a small but definite proportion of abnormal labors.

ETIOLOGY

Those who admit the existence of cervical dystocia offer two general explanations of its origin. The first points to constitutional deficiency manifested by obesity, lack of normal feminine habitus, endocrine dyscrasias, disturbances of menstruation and fertility, and maldevelopment of the vagina, cervix, and corpus uteri. The second theory stresses rigidity and stenosis of the cervix as a result of fibrosis following operative or obstetric trauma, abortions and infections. Since *active* dilatation, retraction, and effacement of the cervix depend upon its intrinsic smooth muscle and autonomic nerves, this function may be weakened by underdevelopment, constitutional and endocrine deficiency. It is further compromised and resisted by scar tissue replacement of the

TABLE II. ETIOLOGIC FACTORS IN CERVICAL DYSTOCIA, 86 CASES

Parity: First full-term pregnancy in 78 cases
Age: 35 years or more in 13 cases. Average 28.3 yr.
Late menarche:
At or after 15 years: 20
At or after 16 years: 11
Irregular menses: 5. Severe dysmenorrhea: 7
Sterility (complaint or operation): 8
Interval between marriage and present pregnancy
Over 2 years: 42 Over 3 years: 27
Over 4 years: 17 Over 5 years: 11
Abortions: 12 patients. Induced in 7, spontaneous in 5
Previous operations on cervix: 15
Previous cervical dystocia: 4 (out of 8 multiparas)
Previous radiation: 1 (14 x-ray treatments for menorrhagia)
Maldevelopment and disease noted antepartum
Marked obesity: 3 Hypopituitary type: 2
Masculine pelvis (but *no* disproportion): 4
Vagina constricted, underdeveloped: 5
Infantile cervix: 13, with pinhole os in 3 cases
Chronic cervicitis and/or erosion: 8
Laceration and scarring: 7, with cervicovaginal band in 2 cases
Cervical fibromyoma: 1

parenchyma following trauma or disease. This fibrosis also obviously hinders *passive* dilatation by the bag of waters and presenting part.

Evidence supporting both concepts of pathogenesis is found in Table II.

The average age was 28.3 years, 13 patients being over 35 years of age. There was no familial or racial preponderance. In 78 out of 86 cases, this was the first full-term pregnancy. Late onset, irregularity or pain with the menses occurred in about one-fifth of the series. Eight patients had sought advice or been operated upon for sterility; and the interval between marriage and the present pregnancy was prolonged in nearly one-half of the cases. Various operations on the cervix had been done in 15 instances; abortion had been induced in 7 women while 5 others had had spontaneous abortions.

Of the 8 multiparas 4 gave a history of previous cervical dystocia; and cervical lacerations or tough scars were observed ante partum in 7 cases, chronic cervicitis in eight others. Fibrosis following fourteen x-ray treatments for menorrhagia in one case, and a cervical fibromyoma in another were thought to hinder dilatation. Thirteen patients had an underdevelopment of the cervix, five being associated with constricted vagina.

Gonorrheal cervicitis does not necessarily lead to cervical dystocia. A patient of the writer, contracting acute infection in the sixth month of her first pregnancy, went into labor at thirty-nine weeks, was fully dilated within eleven hours and was soon delivered of a 7 pound 12 ounce child. Three years later a second labor was completed in five hours.

The foregoing ante-partum data are derived from 49 of the 86 case charts, some of the remainder being doubtless incomplete. The frequency of the various causative factors may therefore be greater than that suggested by Table II. Certainly the descriptions of the cervix during labor, as summarized in Table III, indicate local pathology in a much larger proportion of the cases. Also as shown in Table VI, cervical dystocia was repeated in subsequent confinements of 3 out of 20 patients, an incidence of 15 per cent compared to the incidence of 1.05 per cent for all confinements.

CHARACTER OF LABOR AND DESCRIPTION OF CERVIX

In Table III an attempt is made to group the data from 86 labor records.

The first stage of labor averaged 38 hours 57 minutes and lasted over thirty hours in 61 cases. The entire labor exceeded 36 hours in 51 cases. Contractions were very strong in 71 patients, moderately strong in 8 others. In only 3 of the 82 reported were they called weak; and in 59 out of 82 they occurred at regular intervals. Their duration was more than 30 seconds in 55, over 50 seconds in 45 cases out of 56 reported.

Various adjectives were used to describe the cervix which was pathologic in type, or abnormal in behavior in every one of the 86 cases. Full dilatation was finally achieved in only 19 patients, and 10 cm. in an additional 7. In the remaining 60 women, intervention was necessary with the cervix dilated from nothing to 9 cm.

DIAGNOSIS

Cervical dystocia was suspected if, notwithstanding frequent contractions, definite progress had not occurred in a reasonable time. This presumption was strengthened by a history or clinical findings of disease, injury or underdevelopment of the cervix; and confirmed when examination excluded primary uterine inertia, cephalopelvic disproportion and unalterable abnormal presentation, position and attitude of the fetus. Abdominal and rectal examinations often gave misleading impressions.

TABLE III. CHARACTER OF LABOR IN CERVICAL DYSTOCIA

Stage I: Average 38 hours 57 minutes; extremes 10 to 96 hours; 30 hours or more in 61 cases

Stages II and III: Zero or unrecorded in cesarean sections and many operative vaginal deliveries

Total duration of labor: Average 40 hours 12 minutes; extremes 10 to 96 hours; 36 hours or more in 51 cases

First stage contractions: (at their best)	Strong	71 cases	Regular	59 cases
	Moderate	8 cases	Irregular	23 cases
	Weak	3 cases	Not noted	4 cases
	Not noted	4 cases		

Frequency of first stage contractions: (at best)		*Duration* in	
Every 2 min. or less:	29 cases	90 seconds	2 cases
Every 3 min. or less:	31 cases	70 seconds	6 cases
Every 4 min. or less:	6 cases	60 seconds	15 cases
Every 5 min. or less:	16 cases	50 seconds	22 cases
Every 6 min. or less:	1 case	40 seconds	7 cases
Not noted in 3 cases		30 seconds	3 cases
		20 seconds	1 case
		Not noted in	30 cases

Description of the cervix:

Thick, 54; long, 11; cuff, 2; slowly or incompletely effaced, 7; firm or rigid, 33; tough, 9; leathery, 2; wiry, 1; rubbery, 2; cartilaginous, 3; thin, 3; edematous, 9; soft but thick, 14; undilatable, unyielding, 20; dilating very slowly, 34; thin parchment, 6; firm rim, 6; persistent long anterior lip, 9 (persistent posterior lip *not* noted); lacerated, 3; scarred, 2

Final dilatation achieved:

Fully, 19; 10 cm., 7; 9 cm., 6; 8 cm., 8; 7 cm., 5; 6 cm., 7; 5 cm., 7; 4 cm., 5; 3 cm., 7; 2 cm., 10; 1 cm. or none, 5

Therefore vaginal examinations were indispensable and had to be repeated at fairly frequent intervals to determine progress.

PROPHYLAXIS

Early marriage and pregnancy, good hygiene and control of diseases of the genital organs should prevent some cases of cervical dystocia. Others can be avoided by reduction of trauma due to radical obstetrics, induced abortions, indwelling pessaries, coagulation, amputation, and tracheloplasty. Of all these, the Sturmdorf tracheloplasty gives the lowest incidence of subsequent stenosis and cervical dystocia, according to Bullard's study.[1]

MANAGEMENT

The choice was often difficult between watchful waiting and surgical intervention, between stimulation and sedation, between vaginal and rectal examinations or abstention from such examinations, between abdominal or vaginal delivery, and between the various surgical procedures. The conduct of labor is reviewed in Tables IV and V, the former concerned with the handling of the cervix, the latter giving the method of delivering the child. Individual case records yield the impression that the best results were obtained in those patients who had maintenance of fluids and nutrition, good elimination, and sedation and

TABLE IV. AIDS TO CERVICAL DILATATION

Stimulation:	*Sedation and analgesia:*
Enemas, 81	Morphine and scopolamine, 42
Castor oil, 1	Morphine and scopolamine plus rectal ether, 12
Quinine, 3	Barbiturates alone, 2
Clyses, 19	Barbiturates and scopolamine, 16
Pituitary drugs, 6 (Dangerous!)	Barbiturates and scopolamine plus rectal ether oil, 3

Vaginal examinations:	*Rectal examinations:*
None in 4 cases	None in 20 cases
1 in 11 cases	1 in 15 cases
2 in 12 cases	2 in 15 cases
3 in 16 cases	3 in 21 cases
4 in 18 cases	4 in 8 cases
5 in 16 cases	5 in 5 cases
Over 5 in 9 cases	6 in 2 cases

Operative maneuvers during first stage

None in 71 cases; manual dilatation, 5; bag, 8; manual dilatation plus bag, 2

Operative maneuvers during second stage

Manual dilatation, 16; high forceps, 2; incisions of cervix, 2 (midpost. lip, 1; midant. lip, 1); medium "A" forceps, 18, with cervix pushed up in 8 cases.

Note: Full dilatation and effacement *awaited* in 18 other cases of which 10 were delivered by medium "B" and 8 by low forceps.

TABLE V. METHOD OF DELIVERY

Laparotrachelotomy		36	
Extraperitoneal (Latzko)		8*	
Midclassical		1	
Total cesarean sections			45
High forceps		2	
Medium forceps		28	
Mid "A"	18†		
Mid "B"	10		
Low forceps		9	
Total forceps			39
Version and extraction			1
Decomposition and breech extraction			1
Total cervical dystocia cases			86

*One of these followed attempted mid "A" forceps. Mother and baby living and well.

†Cervix pushed up during traction in 8 of these.

analgesia sufficient to induce sizable rest periods. This rest was often followed by stronger, better spaced contractions and real progress in the cervix. Dilatation and effacement seemed to be furthered, and were certainly more accurately observed by vaginal than by rectal examinations.

First Stage.—One of three main lines of treatment was followed: first, elective cesarean section for those patients where the cervix was so scarred, diseased, or congenitally maldeveloped as to preclude vaginal delivery with safety. Second, the

expectant treatment was tried in all patients where serious medical complications could be excluded. Development of tonic uterus, contraction ring, or maternal or fetal exhaustion led to intervention. Otherwise the labor was allowed up to full dilatation under adequate sedation and analgesia, which seemed to reduce spasm of the lower uterine segment and cervix. Best results were obtained by morphine and scopolamine and by rectal ether-oil mixtures, with or without the aid of barbiturates.

Third, when progress was unsatisfactory under expectant treatment, various operations were used to expedite cervical dilatation and effacement (Table IV). In the first stage of labor, the Voorhees' bag was used in 8 patients, manual dilatation in 5, and the two in conjunction in 2 cases, with more or less benefit. Elder clinicians such as Painter and W. A. Morgan did not hesitate to manually dilate while examining the cervix.

It was sometimes impossible to determine failure of the above measures in time to perform the ordinary types of cesarean or vaginal delivery with safety to mother and baby. It is here that the extraperitoneal cesarean section played an important role in two ways: by permitting longer test of labor and hence more vaginal deliveries; and by salvaging the misjudged case with the results noted below.

Second Stage.—Before vaginal delivery, various maneuvers were used to overcome the resistance of the cervix. Manual dilatation by the Harris method or by digital stretching over the presenting part was done in 16 of the 41 patients delivered per vaginam. In the so-called medium "A" forceps, applied *inside* the cervix, dilatation was gradually wrought by the head plus the blades, aided by pushing the cervix up over the head while the latter was immobilized by gentlest traction. DeLee[8] has truly said that most so-called manual and instrumental dilatations are in reality incisions or tears made with a blunt instrument. It does not follow that Dührssen's incisions are preferable. The tension made by the forceps, or head in the forceps, or by the fingers pushing the cervix over the immobilized head is distributed over the *entire circumference* of the cervix up to the limit of its endurance. Thus lacerations are obviated or minimized; if Dührssen's incisions have to be added, their extension is less likely. In the 18 medium "A" forceps cases noted in Table IV, incisions of the cervix were not performed and post-partum repairs of the cervix were either shortened or entirely unnecessary.

Third Stage.—Examination for and repair of damage is important and here palpation is inadequate. Table VI shows many lacerations discovered only at follow-up visits. Inspection under good light with suitable retractors reveals injuries, permits immediate repair, corrects or rules out one cause of post-partum hemorrhage, reduces the area for entry of infectious organisms, and increases our knowledge of cervical dystocia and the best method for its management.

PROGNOSIS

End-results listed in Table VI give a maternal mortality of 1.2 per cent in 86 cases, 2.2 per cent among cesarean sections and none in 41 vaginal deliveries. On the other hand (Table VII) 1 stillbirth and 3 neonatal deaths, all following difficult forceps operations, give a fetal mortality of 4.7 per cent for the entire series and 10.3 per cent in 39 forceps deliveries. The extraperitoneal cesarean section, despite employment in relatively unfavorable circumstances, was successful in 7 out of 8 cases. With more widespread use, its mortality is decreasing as seen in the following reports:

1930	Steele[2]	8.5% in 59 cases
1930	Nürnberger[3]	5.0% in 60 cases
1932	Sackett[4]	7.8% in 51 cases
1937	Aldridge[5]	3.7% in 27 cases
1937	Norton[6]	1.7% in 58 cases
1939	Barrett[7]	2.9% in 34 cases

While subsequent labor was easy in 13 out of 20 patients, cervical dystocia was repeated in 3 (15 per cent), and elective cesarean section in the remaining 4 was performed for fear of its repetition. Although modern chemotherapy will reduce morbidity and infection, the other maternal and fetal complications listed in Tables VI and VII indicate how serious is the choice between abdominal and vaginal delivery.

TABLE VI. MATERNAL END-RESULTS

Deaths: One (1.2 per cent) on tenth day after extraperitoneal cesarean section following 55-hour labor. Pelvic and wound infection, thrombosis, coronary embolism, and circulatory collapse.
Mild uterine infection: ("sapremia") 14
Infections of perineum or vaginal wall 6 in 41 deliveries
Abdominal wound infections, 7 in 10 cesarean sections:
Laparotrachelotomy, 2 in 36 cases
Extraperitoneal, 5 in 8 Latzkos, all drained
Mastitis, 3; *pyelitis,* 5, *cystitis,* 1; *bronchopneumonia,* 1; *pleurisy,* 1; *pelvic phlebitis,* 1; *saphenous phlebitis,* 2; *post-partum hemorrhage,* 1; *puerperal psychosis,* 1
Lacerations of the cervix:
Discovered during delivery, 20:
stellate, 2; bilateral, 7; right, 7; left, 4
Immediately repaired, 16:
stellate, 1; bilateral, 6; right, 7; left, 2
Discovered in follow-up, 26 lacerations; erosions, 3; cervicitis, 2
Untraced, 27 cases
Subsequent confinements: 22 in 20 patients
Easy labors, with rapid first stage, 15 in 13 patients
Repeated cervical dystocia, 3 cases
Elective repeat cesarean sections, 4

TABLE VII. FETAL END-RESULTS

Birth weight: Average 7 pounds 11 ounces. Only 8 babies over 9 pounds Extremes 5 pounds 7 ounces to 10 pounds 6 ounces
Living, 85; *Stillbirth,* 1, 8 pounds, macerated, cord 2 loops about neck
Neonatal deaths, 3, as follows:
(1) High forceps, 7 pounds 6 ounces, marked asphyxia, died in 10 hours. Cerebral hemorrhage. This patient subsequently had 8-pound 5-ounce living baby after labor of 9 hours 11 minutes, first stage 7 hours.
(2) Medium "A" forceps, 8 pounds 14 ounces, heart beat 15 minutes. Autopsy revealed lacerated falx and tentorium, and subdural hemorrhage.
(3) Medium "A" forceps, 7 pounds 2 ounces, marked molding and asphyxia. Autopsy revealed no hemorrhage or syphilis. Pathologic diagnosis was mature infant; status thymolymphaticus; atelectasis.
Asphyxia, 5; marked molding, 3; birth palsy, 1; cephalhematoma, 1.
Feeding of 82 surviving infants: Breast, 36; bottle, 44; not noted, 2.

SUMMARY AND CONCLUSIONS

1. True cervical dystocia was found in only 86, or 1 per cent of 8,213 confinements at or near full term. Its incidence rose to 13.4 per cent of prolonged labors; it was the major indication for cesarean section in 9.5 per cent, for medium forceps in 3.6 per cent, and for low forceps in 1.7 per cent of such operations.

2. A review of possible etiologic factors points to the occurrence of cervical dystocia in two types of patients: first the elderly primigravida with menstrual and marital history, general habitus and local findings suggestive of constitutional deficiency and genital underdevelopment. In 78 patients this was the first full-term pregnancy, and of the 8 multiparas 4 had had previous cervical dystocia.

The second type presents history and objective evidence of trauma or disease affecting the cervix. Its abnormal condition or behavior is discovered ante partum (Table II) or intrapartum (Table III), and often confirmed in subsequent confinements by repetition of cervical dystocia in at least 15 per cent. This high incidence compares with 1 per cent among full-term confinements in general.

3. The clinical picture of cervical dystocia is characteristic, as shown by the labor records of 86 cases. In reaching a decision as to diagnosis and treatment, vaginal examinations at reasonably frequent intervals are indispensable. Where the cervix is stationary, despite strong contractions, it is better to intervene before local congestion and edema, maternal or fetal distress make the outlook unfavorable.

4. It follows that vaginal delivery in cervical dystocia often involves application of the forceps blades to the head inside a cuff of cervix. Such cases are designated medium "A" forceps to distinguish them from medium "B" forceps in which the cervix has retracted out of the way. This classification leads to more accurate diagnosis and comparison of different methods of treatment.

5. In 41 vaginal deliveries, the cervix was incised only twice, and not at all in 18 medium "A" forceps operations. Combined digital and forceps dilatation usually obviates these incisions; and if they have to be added, their extension is less likely.

6. In the period of 1930 to 1935, inclusive, the employment of cesarean section for cervical dystocia has increased, while the use of forceps has decreased, and for two reasons: First, the condition has been recognized and feared and laparotrachelotomy performed *earlier* in labor. Second, where the decision was made *late* in labor and in cases where transperitoneal operation would be hazardous, the extraperitoneal cesarean section has been increasingly used in place of forceps or craniotomy.

7. The extraperitoneal cesarean section by the method of Latzko, despite its use under relatively unfavorable circumstances in 8 cases, had a favorable outcome for all babies and all but one mother. Citations from the literature indicate that with more widespread use its results have improved. Of equal importance is the possibility of its employment late in labor, which permits a longer test of labor and, hence, more deliveries per vaginam.

8. Maternal and fetal mortality, morbidity, and complications are more frequent in cervical dystocia than in average labors; and the operative incidence is much higher. In view of this a plea is made for more conservatism in the medical and surgical treatment of injuries and disease of the female genital tract in the childbearing age.

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PROPHYLACTIC EXTERNAL CEPHALIC VERSION*

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THE incidence of breech presentation has been shown to be between 2.3 and 4 per cent.[1, 7] The fetal mortality from breech delivery varies in reported series[1-3, 8-11] from 6.9 to 25 per cent. When this figure is compared with a fetal mortality (excluding abortions and nonviable fetuses) of 4.1 per cent, which was reported by the Boston Lying-in Hospital for 1939,[12] it is at once apparent that any procedure which reduces the incidence of breech presentations is worth while. For this reason the maneuver of external cephalic version was instituted as a routine procedure for all breech presentations from the twenty-eighth week of pregnancy to term in the prenatal clinics of the Boston Lying-in Hospital for a period of four years.

Randall[13] reports this maneuver was mentioned by Hippocrates and practiced by the ancients. Bartholomew[14] reviewed briefly the history of version and states that Wiegand in 1807 revived the practice but limited it to oblique and transverse presentations only, whereas Mattei first extended the indication to breech presentations, and to Pinard belongs the credit of popularizing the operation. In recent years Ryder,[8] Siegel and McNally,[15] Cannell and Dodek,[11] Mehta,[4] Bartholomew,[14] Glassman,[16] and many others enthusiastically endorse its routine employment and report between 75 and 90 per cent success.

At the Boston Lying-in Hospital during the years in which the study was made, an average of 3,487 patients were delivered each year in the hospital and in the out-patient department, so that in all, 13,948 were seen.

The procedure followed was palpation of each case at the twenty-eighth, thirty-second, and thirty-sixth week of pregnancy. If a breech were detected, version was attempted and the case was then followed at weekly intervals until the vertex presentation had persisted for three weeks. If the breech presentation recurred or version was unsuccessful additional attempts were made. Anesthesia was employed in selected cases, such as in primiparas with contracted pelves and when it was felt that the resistance of the skeletal musculature was the factor in making the version difficult.

Although several obstetric textbooks describe the maneuver in this series, no set procedures were carried out. The patient's bladder was

*Read at a meeting of the Obstetrical Society of Boston, March 18, 1941.

emptied and, if possible, the rectum. Lifting the breech well up from the pelvis and moving it to one side or the other before bringing the head down was found to be essential. If possible, the baby was rotated so that the flexion was preserved, but if there was less resistance, rotation in the opposite direction was used. Elevation of the foot of the table as first suggested by Frühinholz[17] in 1904 to an angle of 45 degrees is helpful to disengage the breech from the pelvis. In some cases it was necessary to push the breech up by a finger inserted in the rectum. No pads or bindings were employed to maintain the vertex presentation once it had been established.

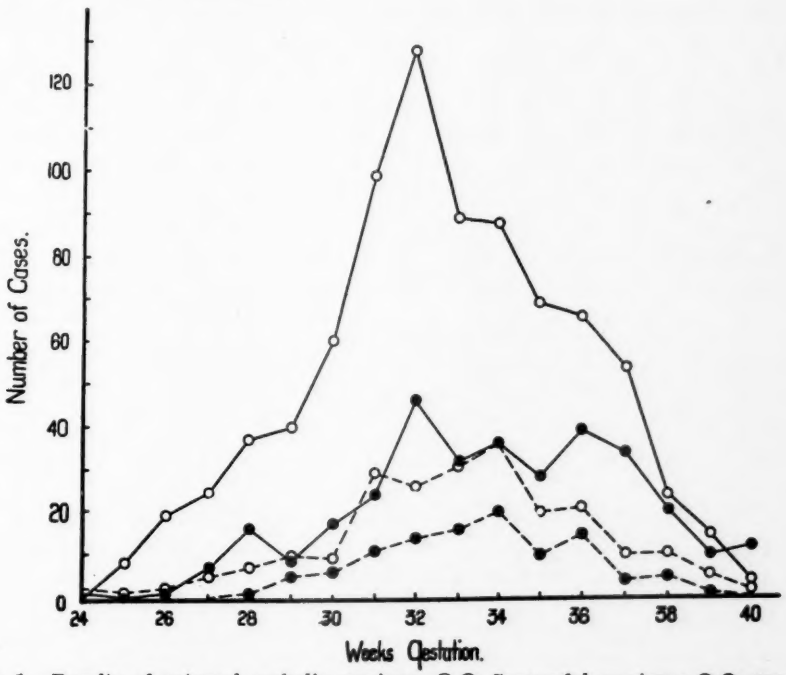

Fig. 1.—Results of external cephalic versions. ○-○, Successful versions; ●-●, unsuccessful versions; ○---○, recurrent breech presentations; ●---●, spontaneous versions.

In general, it may be said that external cephalic version is indicated in all cases during the last trimester of pregnancy, unless any of the following conditions exists:

1. Multiple pregnancy.
2. History of vaginal bleeding.
3. History of previous myomectomy and abdominal hysterotomy.
4. Marked deformities of the fetus, such as hydrocephalus and anencephalus.
5. Marked pelvic contraction.

In slight and moderate degrees of pelvic contraction, a vertex presentation is of great value as it permits the patient a test of labor.

The diagnosis of breech presentation was made in 793 cases in a total of 13,948 patients, or 5.6 per cent, from the twenty-fourth week of pregnancy to term. Of this number 241, or 30.4 per cent, were primiparas. A total of 1,161 versions were attempted, or 1.46 versions per case.

This figure is explained by the fact that extra attempts at version were necessary when the breech recurred and when the initial attempts were unsuccessful. Version was successful in 829 cases, or 72 per cent. At term only 20.8 per cent of the primiparas and 6.4 per cent of the multiparas presented breeches (50 per cent and 35 per cent, respectively). Recurrence to breech presentation occurred in 224 of the successful versions, or 27 per cent. Spontaneous version occurred 108 times, or 19.35 per cent, in those cases in which attempted version was unsuccessful or in which recurrence of a breech presentation occurred.

These figures are shown in Fig. 1.

It may be seen that the greatest number of successful versions were performed in the thirty-second week. The successful and the unsuccessful attempts roughly parallel each other in a ration of about 3 to 1 until the thirty-fourth week after which, as term is approached, they come together. This would be expected for version becomes more difficult as the fetus increases in size, the uterus becomes more spastic and the abdominal wall more tense, all of which occur as term is approached. The recurrence of breech presentations and spontaneous versions also roughly parallel each other with the maximum number of each occurring at the thirty-fourth week and a ratio of about 2 to 1 holding throughout.

The presentation at the onset of labor for the 793 cases is shown in Table I. Of the vertex presentations, the figures shown in Table II obtained as to position. Table III demonstrates the manner in which these 793 patients were delivered.

TABLE I

	PRIMIPARA		MULTIPARA		TOTAL	
	NO.	%	NO.	%	NO.	%
Vertex	190	78.8	518	94.0	709	89.5
Breech	42	20.3	31	5.6	80	10.1
Transverse	1	0.4	2	0.4	3	0.3
Face	1	0.4	0	0.0	1	0.1
Total	241		552		793	

TABLE II

	L.O.A.	L.O.T.	L.O.P.	R.O.A.	R.O.T.	R.O.P.
No.	159	34	49	100	26	48
%	38.2	8.2	11.7	24.0	6.2	11.0

TABLE III

	PRIMIPARA		MULTIPARA		TOTAL	
	NO.	%	NO.	%	NO.	%
Normal	107	44.4	492	89.1	599	75.7
Low forceps	78	32.3	12	2.4	90	11.3
Breech	42	17.4	31	5.6	73	9.2
Section	14	5.8	11	2.0	25	3.1
I.P.V. and Braxton Hicks	0	0	6	0.9	6	0.7
Total	241		552		793	

As may be seen in Table III, 25 patients, or 3.1 per cent, were delivered by cesarean section. Of this number the indication for 7 was primiparous breech with pelvic contracture, 1 transverse presentation in a primipara, and for 1 face presentation in a primipara. The indication in the remaining 16 cases was about equally divided between bleeding and cephalopelvic disproportion. It is interesting

to note that DeNormandie[18] found an increase in the incidence of sections with the indication of primiparous breech in his survey of cesarean sections in Massachusetts in 1939. The maternal mortality was zero, no patients having died because of this manipulation or from any other cause. The gross fetal mortality including macerated, stillborn, and neonatal deaths for this series was 32, or 4.03 per cent, which compares favorably with the gross fetal mortality of the Boston Lying-in Hospital.[12] Table IV shows the distribution of the deaths.

TABLE IV

	STILLBIRTHS		NEONATAL DEATHS	
	DELIVERY	NUMBER	DELIVERY	NUMBER
Term	VVVVV* BBBBB	10	VVVVV B	6
Premature	VVVVV TT	7		0
Congenital anomolies	VVVV B	5	VVV F	4
Total		22		10

*V, Vertex; B, breech; T, twin; F, face.

Subtracting the 9 cases where the cause of death was gross fetal anomalies, the corrected mortality was 23, or 2.9 per cent. Two of these deaths were accounted for by separation of the placenta ten days following an attempt at version with a twin pregnancy. In 6 cases, death followed breech extraction where version had been unsuccessful.

The most frequent complications resulting from version, mentioned in the literature, are fetal death due to some interference with the circulation of the cord or some degree of separation of the placenta. McCullagh[19] reported 4 cases of rupture of the uterus during labor due to neglected compound presentations. In these cases antenatal version had been performed on frank breech presentation, and the legs had remained extended.

In this series the complications are considered under three headings. Those occurring because of some interference with the cord circulation; cases in which antenatal bleeding occurred; and stillbirths following version in which no cause could be determined.

The cord was found about the neck in 66 cases, or 8.3 per cent. In 2 cases, fetal distress developed during labor due to this complication, but living babies were delivered. In only 1 case did stillbirth result, the cord being tightly about the neck 2 times. Another stillbirth was attributed to a true knot in the cord. There were 4 cases in which the cord prolapsed during labor, and 2 cases in which the cord was around one or more of the extremities. Living babies were delivered in all 6 cases. In only 4 cases out of the entire series, or 0.5 per cent, was it necessary to restore the breech presentation because the fetal heart was slowed and irregular after cephalic version. Spotting in small amounts occurred in 7 cases. In 2 of these cases, the spotting appeared directly after version. In the remaining 5, the spotting appeared from one to six weeks after the version. All 7 babies were born alive. The diagnosis of separation of the placenta was made four times. In 3 cases the separation occurred nine, eight, and seven weeks, respectively, after the version, and all 3 babies were born alive. In the fourth case, version was attempted on a multiple pregnancy through mistaken diagnosis in the thirty-fifth week of pregnancy. One week later partial separation of the placenta occurred, both babies being born alive but died soon after birth.

There were 5 patients from whom macerated babies were delivered. In all of these cases there were no demonstrable causes of death. Delivery was effected at 2, 3, 6, 6, and 6 weeks, respectively, after version, and in each case the fetal heart was known to be normal one week after version.

Anesthesia has been employed by various men but, for the most part, has not been enthusiastically indorsed. In fact, many of the serious complications reported have resulted from the use of too much force while the patient was under an anesthetic.

In this series, anesthesia was used in selected cases when a vertex presentation was particularly desirable and when it was felt that lack of cooperation in securing relaxation of the abdominal muscles could best be circumvented by this method. In all, anesthesia was employed 48 times, of which 18 versions were successful. Inhalation of nitrous oxide, oxygen, and ether was used in 12 cases, while intravenous administration of evipal or pentothal was used in the other 36. The latter type was more satisfactory, as it required no preliminary medication and the patients were ambulatory in a much shorter time.

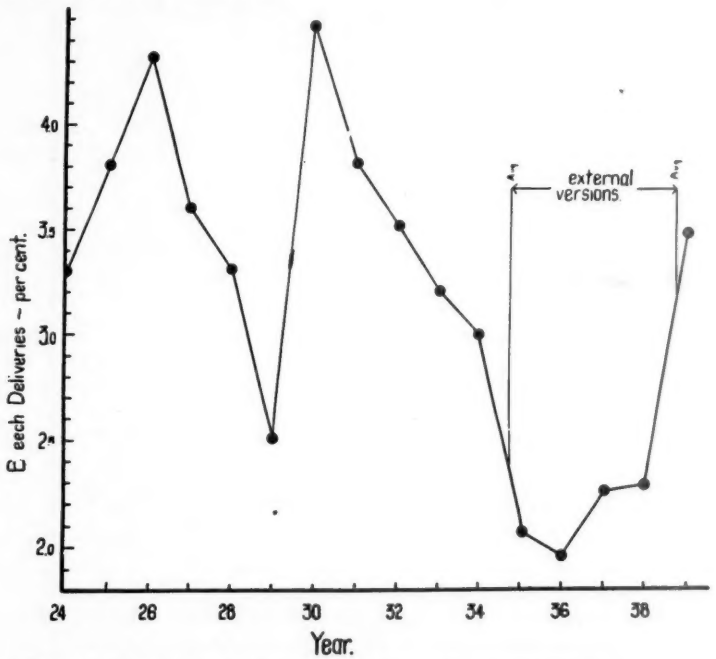

Fig. 2.—Incidence of breech deliveries, 1924-1939. Percentage of total deliveries plotted chronologically. The period, August, 1934 to August, 1938, when external versions were routine is indicated.

As so little is known concerning the reason for breech presentation, it was thought of interest to tabulate the cases of patients in whom any cause could be determined as well as the cases of patients who had previously been delivered of breech presentations. There were only 17 of the latter, or 2.2 per cent. In 54 patients, or 6 per cent, some cause for the breech presentation was found (Table V).

During the four-year period of this study, there were 246 breech deliveries out of a total of 10,529 hospital deliveries, or an incidence of 2.33 per cent. This figure compares favorably with the breech incidence of 3.75 per cent for the four-year period prior to the routine adoption of external cephalic version. (Fig. 2.)

There is no doubt that the incidence of 2.33 per cent could be lowered when the fact emerges that of 246 breech deliveries which occured, in

TABLE V. CAUSES OF BREECH PRESENTATION

Contracted pelvis	34
Placenta previa	8
Fibromyomas of uterus	4
Congenital malformations	4
Hydramnios	2
Laxity of abdominal wall	1
Cyst of ovary	1
	54

149, or 60.5 per cent, version was not attempted. This paradox is explained when it is found that in 121 cases, or 49 per cent, the diagnosis of breech presentation was not made until the patient was admitted for delivery. This seemingly unusual figure is somewhat improved by the fact that 38 cases were either nonviable or premature babies.

A four-year study of the results of the routine employment of external cephalic version was made. A diagnosis of breech presentation was made in 793 of a total of 13,948 cases, or 5.6 per cent. A total of 1,161 versions, or 1.46 per case, were attempted, 72 per cent being successfully accomplished. The recurrence rate was 27 per cent. Spontaneous version occurred 108 times, or 19.35 per cent, in cases where either recurrence had taken place or version had been unsuccessful. Anesthesia was helpful but was employed only in selected cases. The presentation and type of delivery employed are tabulated for the 793 cases. There was no maternal mortality. The gross fetal mortality was 4.03 per cent. The breech incidence at the Boston Lying-in Hospital was reduced from 3.75 per cent to 2.33 per cent.

External cephalic version employed routinely is a safe procedure and will reduce by more than 38 per cent the incidence of breech presentation with its inevitably high fetal mortality.

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BLOOD CHOLINE VARIATIONS IN PREGNANCY, IN LABOR, AND IN THE PUERPERIUM

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REVIEW OF LITERATURE

THE first extraction of a physiologically active substance from the human placenta was made in 1885 by Böhm,[1] who found an average of 50 mg. of choline per placenta.

Twenty-two years later Rieländer[2] likewise obtained approximately the same result (average 40 mg. of choline per placenta). In the same year (1907), Dixon and Taylor[3] reported that the placenta produces a chemical substance which develops with the ripening of that tissue, the liberation of which by the contracting uterus and vessels might induce the onset of normal labor. In 1928, Sievers[4] confirmed the previously reported choline content of the placenta (average 40-45 mg. per organ) and proposed the theory that the latter tissue stored choline which was transferred to the uterus by pressure on the placenta at the time of birth, thus causing the uterine contractions. Larger amounts of choline in the placenta were reported by other authors (5.0-120.0,[5] 61.0-92.2,[6] 51.5-243.0,[7] 54.0-163.0,[8] 6.0-84.0,[9] 0-945.0,[10] and 102.0-282.0[11]). Smyth[12] has recognized a water-soluble precursor of choline in the human placenta, each molecule of which contains one molecule of choline, one of phosphoric acid, and one amino linkage.

Hauptstein[13] concluded that if choline were to be considered responsible for the uterine contractions during labor, it must be present as the far more powerful acetic ester, acetylcholine, and noted that in 18 cases the placenta contained acetylcholine in amount varying from 74 to 459 mg. per kg. of tissue. From then on, Bischoff and others;[9] Chang and Wong;[14] Wong and Chang;[15] and Wen, Chang and Wong,[16] who found the origin of the free placental acetylcholine to be in the syncytial layer of the villus, reported the following acetylcholine values, respectively: 168-220, 15-133.3, 12.5-133.3, and 19-104 mg. per kg. of tissue. Chang[17, 18] reported (1935) that there is a reserve of acetylcholine in the placenta which may be liberated from its precursor in vitro, and found (1938) that there is a "free" and a "bound" fraction of acetylcholine in the human placenta. Hunt[19] pointed out many years ago that intravenous injection in cats of as little as 0.000,000,0024 mg. of acetylcholine per kg. body weight can cause a pronounced fall in blood pressure. The presence in the placenta of such large amounts of this powerful substance may be more than a coincidence.

That the uterus responds to choline by contraction has been known for some time, particularly since the reports of Müller,[20] Adler[21] and Berlin[22] who pointed out that the effect of choline on the uterus of the cat or mouse simulated the contractions in labor. Engeland and Kutscher[23] have reported that choline causes tetanic contractions of the gravid uterus, and Alberts[24] has stated that the gravid uterus is more sensitive to choline than the nongravid one. In a study of the quantitative action of acetylcholine on the guinea pig uterus, Webster[25] found that the height of contraction varies with the concentration, but even a molar concentration of 4.4×10^{-7} gave good contractions. Sherif[26] showed that acetylcholine acts as the chemical transmitter of the effects of the hypogastric nerves on the uterine muscle, similar to that of the vagi nerves.

The effectiveness of acetylcholine as an oxytocic agent was recently studied in a series of 28 patients.[15] In 7 out of 16 cases in which the membranes were intact,

acetylcholine induced labor and brought about delivery; in the other 9 cases uterine contractions were obtained but did not last long enough to terminate pregnancy. The procedure was successful in inducing labor in all of the 12 cases where the membranes were ruptured spontaneously or artificially, and rhythmic uterine contractions were initiated within a few minutes regardless of whether the patient was a primipara or a multipara.[15] Contractions of the guinea pig uterus after application of blood from women in labor had been noted by Brdiczka[27] and Fontes,[28] and within recent years considerable attention has been directed to the presence of some oxytocic material in the blood of women in labor.

Prior to 1923 most investigators were unable to find free choline in the blood or serum of man or animals. From 1923 to the present the values reported were zero in six instances and in twenty-four others the amounts have ranged from 0.5 to 310.0 mg. per liter. The lowest values on human blood (aside from zero) were obtained by Kahlson[29] (2.2-8.5 mg./liter), and the highest by Vasiliu[30] (18.2-147.0 mg./liter). The inaccuracy and nonspecificity of the methods employed can account for such wide divergence in results. Some of these methods are discussed in connection with a study of the choline content of biologic fluids.[31]

METHOD

The method used in the present study has been described in detail elsewhere.[31] Blood choline determinations were made on venous (arm) blood of women in various stages of pregnancy, labor, and the puerperium at the Chicago Lying-in Hospital or its "Stockyards Dispensary." The analyses were done in duplicate; in some cases even three

TABLE I. BLOOD CHOLINE VALUES DURING PREGNANCY

NO.	AGE YEARS	OBSTET. HISTORY*	DAYS BEFORE DELIVERY	CHOLINE FOUND MG./LITER	NO.	AGE YEARS	OBSTET. HISTORY*	DAYS BEFORE DELIVERY	CHOLINE FOUND MG./LITER
1	22	0,0,0,0	0	12.1	32	27	0,0,0,0	40	15.2
2	19	0,0,0,0	1	15.8	33	23	0,0,0,0	41	11.6
3	22	0,0,0,0	1	10.9	34	43	1,0,0,1	41	13.2
4	26	0,0,0,0	1	15.6	35	31	2,0,0,2	54	13.0
5	24	3,0,3,0	3	10.4	36	34	0,0,0,0	55	11.4
6	25	1,0,0,1	4	10.0	37	29	2,0,0,2	55	16.2
7	18	1,0,1,0	4	13.2	38	32	6,0,2,4	61	11.5
8	27	1,0,0,1	5	12.6	39	19	1,0,0,1	61	13.6
9	21	1,0,0,1	7	12.8	40	35	4,0,2,2	62	12.0
10	24	0,0,0,0	7	12.1	41	28	1,0,0,1	66	12.7
11	18	0,0,0,0	9	12.4	42	29	5,0,0,5	67	11.3
12	28	3,0,0,3	9	14.4	43	25	0,0,0,0	68	10.6
13	23	2,0,0,3	10	12.6	44	24	2,0,0,2	72	14.6
14	22	0,0,0,0	10	11.2	45	18	0,0,0,0	79	13.8
15	23	2,0,0,1	11	11.9	46	41	11,0,0,11	83	9.9
16	28	0,0,0,0	11	19.0	47	23	2,0,0,2	85	13.7
17	30	1,0,0,1	12	12.8	48	27	0,0,0,0	90	12.3
18	21	0,0,0,0	16	15.0	49	19	0,0,0,0	91	10.2
19	38	2,0,0,2	16	13.6	50	31	1,0,0,1	94	10.6
20	23	0,0,0,0	17	14.4	51	35	5,0,0,5	98	19.9
21	26	0,0,0,0	20	12.9	52	21	1,0,0,1	100	10.6
22	27	0,0,0,0	21	12.0	53	24	1,0,0,1	114	11.1
23	19	1,0,0,1	23	13.3	54	31	2,0,0,2	120	14.4
24	23	0,0,0,0	24	12.9	55	22	0,0,0,0	125	16.3
25	31	6,0,0,6	25	11.2	56	22	1,0,0,1	145	14.0
26	21	0,0,0,0	26	15.0	57	21	2,0,0,1	150	15.8
27	23	0,0,0,0	26	11.4	58	27	3,0,0,3	172	12.0
28	27	0,0,0,0	28	16.4	59	23	3,0,1,2	176	12.8
29	28	0,0,0,0	32	11.6	60	24	6,0,5,1	178	13.1
30	23	0,0,0,0	32	11.8	61	22	0,0,0,0	179	14.5
31	27	0,0,0,0	37	14.1	62	22	1,0,0,1	207	13.3

*Previous pregnancies, premature labors, abortions, and children now living.

or four analyses were performed on the same sample. Frequent blank determinations and control analyses were likewise performed. With but few exceptions all of the 87 experimental subjects were in good health. Some of the 18 male and 19 nonpregnant female controls were subsequently admitted to Billings Hospital from the Out-Patient Department (where the latter samples were obtained), but none was gravely ill or in acute distress at the time the blood sample was taken.

RESULTS

Blood Choline in Pregnancy.—Table I records the choline values on venous blood samples taken from 62 subjects at times varying from just prior to the onset of labor to 207 days before delivery. It may be seen that from the third lunar month of pregnancy (197-224 days before delivery) to term there was no significant variation in the average choline values, which for the third to the tenth lunar month inclusive were 13.3, 13.1, 14.9, 13.9, 12.9, 12.2, 13.1, and 13.1 mg. per liter, respectively. The average choline results for 28 primigravidas, 14 secundigravidas, and 20 multiparas were, respectively, 13.3, 12.4, and 13.2 mg. per liter; the grand average for all 62 subjects was 13.1 mg. of choline per liter of blood.

Blood Choline During Labor and Post Partum.—Table II summarizes the data on 17 subjects in various stages of labor. The average choline value for the entire group was 15.0 mg. per liter, somewhat higher than that for blood during pregnancy. Table III shows the post-partum choline results on 8 subjects. In 6 cases in which

TABLE II. BLOOD CHOLINE VALUES IN LABOR

NO.	AGE YEARS	OB-STET. HIS-TORY[a]	TIME SAMPLE HR.-MIN.	DURATION OF LABOR				DUR. OF PREG. WK.	BABY		CHO-LINE FOUND MG./ LITER	DE-LIV-ERY
				STAGES			TOTAL HR.-MIN.		WT. GM.	SEX		
				1ST HR.-MIN.	2ND HR.-MIN.	3RD HR.-MIN.						
63	26	1,0,1,0	6-10[b]				24-30	40	e	M	13.5	e
64	24	0,0,0,0	6-11[b]	13:45	0-51	0- 7	14-43	39	3630	M	18.2	f
65	18	0,0,0,0	7- 0[b]	18-40	1-15	0- 3	19-58	40	4150	F	13.6	g
66	23	2,0,0,2	7- 0[b]	9-35	0-10	0-15	10- 0	40	2800	F	12.8	h
67	30	0,0,0,0	7-10[b]	15- 0	1-17	0- 8	16-25	40	3025	M	21.2	i
68	20	0,0,0,0	7-30[b]	14-35	1-16	0- 9	16- 0	40	3255	F	11.7	j
69	20	0,0,0,0	8-17[b]	14-50	1-53	0- 8	16-51	40	3590	F	18.3	j
70	28	3,0,0,2	8-55[b]	11- 5	0-22	0- 8	11-35	40	3265	F	14.3	h
71	19	0,0,0,0	9- 0[b]	29- 0	1-35	0-12	29-47	40	3360	M	12.4	g
72	34	3,0,0,3	9- 3[b]	11-30	0-31	0-10	12-11	40	4570	M	14.1	h
73	40	5,0,2,3	11- 8[b]	11-15	0-11	0- 4	11-30	40	3840	M	13.7	h
74	28	0,0,0,0	11-43[b]	27-15	1- 8	0- 7	28-30	40	3375	M	22.8	g
75	23	0,0,0,0	19-35[b]	23-55	0-29	0- 6	24-30	40	3245	M	10.7	j
76	27	1,0,0,1	25-58[b]	41- 0	0- 6	0- 4	41-10	41	3955	M	12.2	k
77	27	2,0,1,1	Onset[c]	18-30	0-58	0- 6	19-44	40	3175	F	15.0	j
78	16	0,0,0,0	d	20-55	1-25	0- 2	22-22	38	3460	F	11.9	l
79	25	2,0,2,0	End[c]	7-15	0-37	0- 5	7-58	40	3230	F	19.3	g

[a] Previous pregnancies, premature labors, abortions, children now living.
[b] After onset of first stage of labor.
[c] Second stage of labor.
[d] Seven minutes after onset of second stage of labor.
[e] Twins: I, midforceps, 2,390 Gm., M.; II, breech extraction, 2,375 Gm., M. Acute fulminating toxemia; five convulsions during delivery; placenta removed manually.
[f] Forceps rotation; low forceps with episiotomy.
[g] Spontaneous delivery with episiotomy.
[h] Spontaneous delivery.
[i] Mild toxemia; spontaneous delivery with episiotomy.
[j] Low forceps with episiotomy.
[k] Midforceps with episiotomy.
[l] Manual rotation; low forceps with episiotomy.

TABLE III.—POST-PARTUM CHOLINE VALUES

NO.	AGE YEARS	OBSTET. HISTORY[a]	SAMPLE: TIME AFTER DELIVERY HR.-MIN.	DURATION OF LABOR				DUR. OF PREG. WK.	BABY		CHOLINE FOUND MG./LITER	DELIVERY
				STAGES			TOTAL HR.-MIN.		WT. GRAMS	SEX		
				1ST HR.-MIN.	2ND. HR.-MIN.	3RD HR.-MIN.						
80	25	2,0,2,0	0-10	7-15	0-37	0- 6	7-58	40	3230	F	24.9	b
81	18	0,0,0,0	0-10	33-35	1-35	0-13	34-10	40	2970	F	22.9	b
82	21	0,0,0,0	1-16	7-30	0-34	0-21	8-25	41	3095	M	19.0	b
83	18	0,0,0,0	1-17	5- 0	1-51	0- 2	6-53	40	2575	F	30.7	c
84	33	1,0,1,0,	2-10	38-53	1-20	0- 8	40-21	36	3040	F	25.9	e
85	34	10,0,0,10	4-15	8-15	0-14	0- 7	8-36	41	3520	F	24.0	f
86	27	5,0,0,5	44 days	----	---	---	2-10	40	3859	M	13.4	d
87	33	6,0,0,5	48 days	----	---	---	6- 0	40	4545	F	11.3	f

[a]Previous pregnancies, premature labors, abortions, children now living.
[b]Spontaneous delivery with episiotomy.
[c]Manual rotation; spontaneous delivery with episiotomy.
[d]Unattended labor.
[e]Midforceps with episiotomy.
[f]Spontaneous delivery.

blood was taken within 255 minutes after delivery, the average choline content was 24.6 mg. per liter. The significance of this marked rise in the choline content of maternal (venous) blood immediately after delivery of the placenta is not fully understood, and its explanation must await further knowledge of the role in the organism of choline and its esters which already enjoy unique distinction as a hormone and an essential food factor. Two subjects who were forty-four and forty-eight days post partum showed low or normal blood choline values (13.4 and 11.3 mg./liter).

The average choline content of the venous blood of 18 male subjects was 13.4 mg. per liter; that for 19 nonpregnant female subjects was 14.6 mg. per liter. The ages and diagnoses on these 37 individuals varied widely.

Neither in pregnancy, in labor, nor in the puerperium was there any obvious correlation between the choline content of the blood and the previous obstetric history, the age of the mother, the total duration of pregnancy, the duration of the various stages of labor, the weight or sex of the child, the weight of the placenta or the manner of delivery.

COMMENT

In 1932 Jeffcoate[32] proposed the theory that estrin is essential for parturition, an idea which has been supported by the observations that estrin causes contractions of uterine muscle,[33-35] and that estrin is present in considerable quantity during pregnancy, reaching its peak at the time of parturition.[36] Witherspoon[37] suggested that an inhibitory action on estrin (by the luteinizing factor in the ovary, placenta and anterior lobe of the hypophysis) which is present during early pregnancy is released toward the end of gestation, and an increased sensitivity of the uterus to pituitrin produces uterine contractions until delivery occurs. A theory involving the excitatory action of some hormone on the numerous ganglia of the uterus leading to contraction of that organ was advanced by Gibbons[38] who indicated that there remained only the discovery of something sufficiently powerful to excite the uterine ganglia to produce these essential contractions. The recent observation that the acetylcholine content of the uterus significantly increased within an hour after injection of estrin and completely disappeared after twelve hours is of interest in this connection.[39]

In a study of the choline content of the saliva during the menstrual cycle, Eagle[31] found that the choline value showed a cyclic variation, the maximum deviations from the lowest level for each of four subjects being 396, 294, 226, and 398 per cent, respectively. The choline curves showed peaks occurring on the second to seventh day, on the thirteenth to sixteenth day, and on the twenty-second to twenty-fourth day of the cycle, all of which are periods of considerable uterine activity. The results in the present study likewise indicate an elevated choline content of the blood (immediately following the delivery of the placenta) at a period of great uterine activity.

It will be recalled that choline and acetylcholine are normal constituents of the body; that the latter, which is recognized as the chemical transmitter of the effects of the hypogastric nerve on uterine muscle, is a powerful oxytocic agent causing rhythmical contractions of the uterus in man and animals; that the gravid uterus is more sensitive to choline and acetylcholine than the nongravid one; that the acetylcholine content of the uterus may be increased by estrin injection; and that the choline content of the blood and saliva is markedly elevated during periods of great uterine activity. On the basis of the foregoing, it is concluded that, whatever be the cause or causes of the onset of labor, the possible role of choline and its powerful esters in facilitating the emptying of the uterus at term should be considered.

SUMMARY

1. Choline determinations were made on blood samples from 62 women in various stages of pregnancy, 17 women in labor, 8 women in the puerperium, 19 nonpregnant females, and 18 males, a total of 124 samples.

2. The choline content of the blood from pregnant women is fairly constant from 207 days before delivery to term (average 13.1 mg./liter).

3. The blood choline value is slightly increased during labor (average 15.0 mg./liter).

4. The choline level is highest just after delivery (average 24.6 mg./liter). In two cases which were 44 and 48 days post partum, the choline results were 13.4 and 11.3 mg. per liter.

5. An average of 14.6 mg./liter was obtained for the choline content of blood from nonpregnant female patients; that for male patients was 13.4 mg. per liter.

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THE CLOTTING MECHANISM OF MENSTRUAL FLUID*

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THE fact that the menstrual discharge of normal women contains noncoagulated blood has aroused much study and speculation. The excellent reviews by Pickering,[1] Bartelmez,[2] and Dogliotti[3] indicate the numerous hypotheses that have been presented in explanation of this phenomenon. Four main factors have been variously regarded as being responsible for the presence of noncoagulated blood in menstrual blood. These may be summarized as follows:

1. The presence of an anticoagulant.[4-6]
2. A disturbance in the peripheral circulating blood.[7]
3. The presence of a lytic agent which dissolves the clot after it forms in the uterine cavity.[5-11]
4. The absence of one or more elements essential for the coagulation of normal blood.[3, 12-17]

As may be anticipated, agreement between the findings of the different investigators is wanting, and even among those supporting the same hypothesis there rarely is complete accord. Because of the many conflicting concepts and the recent development of more efficient methods for the study of blood coagulation, we believed it pertinent to reopen the problem.

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EXPERIMENTAL

Menstrual fluid was collected during the night into a clean dry Ramses spring type pessary for from six to eight hours. All subjects studied were normally menstruating, healthy females. Fourteen experiments were performed on 9 subjects in from one to two hours after collection of the menstrual fluid. When the same subject was studied on more than one occasion, the menstrual fluid was collected during different menstrual cycles. Occasionally the fluid became layered, in which instances the superficial layers were employed.

Fibrinogen was prepared by a modification of the method of Smith, Warner and Brinkhaus,[18, 19] in that, aside from dialysis, the preparation was made at room temperature. All reagents used were stored in the ice box. The plasma utilized was obtained from a human blood bank and contained 50 ml. of 2½ per cent sodium citrate to 500 ml. of blood. The plasma was centrifuged for thirty minutes at 2,500 r.p.m. until all the red blood cells were removed. To each 100 ml. of plasma, 10 ml. of colloidal magnesium hydroxide were added with constant stirring. After standing for ten minutes, the plasma was centrifuged at 2,500 r.p.m. for twenty minutes. In this manner the plasma was made prothrombin free. To the plasma was now added approximately one-fourth volume of saturated ammonium sulphate to produce a heavy flocculation and clumping of the fibrinogen. Occasionally, an additional 2 to 3 ml. of ammonium sulphate were found necessary. The mixture was centrifuged and the precipitated fibrinogen was redissolved in a volume of oxalated saline equal to that of the original plasma volume. The fibrinogen was again precipitated with one-fourth the original plasma volume of saturated ammonium sulphate. If the amount of precipitate seemed scanty, 3 to 5 ml. of additional ammonium sulphate were added. After centrifuging, the fibrinogen was dissolved in one-tenth the original plasma volume of oxalated saline, and dialyzed in the ice box against frequently changed oxalated saline, until the dialyzing solution gave no test for SO_4 ions with $BaCl_2$. The final yield of fibrinogen was then stored in the ice box in 2 ml. portions. More recently, 1 ml. portions were lyophilised as suggested by Ferguson.[20] Such a preparation of fibrinogen is still active after two to three months.

Thromboplastin, prepared by a modification of the method of Quick[21] was employed in all these experiments. Activated serum was used as the thrombin solution. In order to minimize the effect of antithrombin, fresh thrombin, in the form of activated serum, was used for each phase of the experiment. To prepare this activated serum, one part of 0.28 per cent $CaCl_2$ was added to a mixture of one part of Quick's thromboplastic solution and one part of fresh oxalated plasma. The latter was prepared by mixing 1 c.c. of 1.34 per cent sodium oxalate with 9 c.c. of blood in a 10 by 75 mm. test tube. The clot which formed in fifteen to twenty-five seconds was rolled out, and the serum used immediately.

In each experiment, the menstrual fluid was tested for the presence of thrombin, fibrinogen, prothrombin, and anticoagulants. The experiments were carried out in a 10 by 75 mm. test tube and maintained at 37.5° C. in a water bath. In each experiment, the fibrinogen was tested for the presence of prothrombin by the addition of equal quantities of thromboplastic solution and calcium. Only solutions which contained no prothrombin, or minute traces of prothrombin, were used. All experiments were carried out in duplicate.

To test for thrombin, fibrinogen was added, since that should cause the coagulation of menstrual fluid in the presence of thrombin. To 0.1 ml. of menstrual fluid was added 0.1 ml. of fresh fibrinogen solution. Incubation at 37.5° C. for sixteen to eighteen hours did not produce coagulation in any instance.

To test for fibrinogen, menstrual fluid was tested with freshly prepared thrombin, since in the presence of fibrinogen this procedure should produce a coagulation of the menstrual blood. To 0.1 ml. of menstrual blood was added 0.1 ml. of freshly

prepared thrombin solution. In no case did coagulation occur after incubation at 37.5° C. for sixteen to eighteen hours.

To eliminate the presence of a thrombin or fibrinogen inhibitor, 0.1 ml. of freshly prepared thrombin was added to a mixture of 0.1 ml. of fibrinogen solution and 0.1 ml. of menstrual fluid. Coagulation always occurred within twelve to fifty-five seconds (Table I). As a control, 0.1 ml. of freshly prepared thrombin was added to a mixture of 0.1 ml. of saline and 0.1 ml. of fibrinogen. In every case, the tubes containing menstrual fluid showed no delay in coagulation as compared with the saline controls. In fact, in many instances coagulation seemed slightly accelerated in the presence of menstrual fluid, which is in accord with the observations of others.[3, 14, 16] This experiment suggests that a thrombin inhibitor is not present in the menstrual fluid.

TABLE I. THE INFLUENCE OF MENSTRUAL FLUID ON COAGULATION

SUBJECT	TEST NUMBER	SALINE CONTROL* SECONDS	MENSTRUAL FLUID† SECONDS
A	1	24	21
	2	23	23
	3	21	19
B	4	18	18
	5	24	24
C	6	60	55
	7	13	14
D	8	17	16
	9	14	12
E	10	19	16
F	11	25	24
G	12	27	24
H	13	39	36
I	14	33	31

*0.1 ml. saline + 0.1 ml. fibrinogen + 0.1 ml. thrombin.
†0.1 ml. menstrual fluid + 0.1 ml. fibrinogen + 0.1 ml. thrombin.

It may be noted from Table I that there is much variation in the coagulation times of the various tests. This may be due to the instability of the reagents, since the controls always give similar results.

To test for the presence of prothrombin, 0.1 ml. of fibrinogen solution was added to a mixture of 0.1 ml. of Quick's thromboplastic substance and 0.1 ml. of calcium and menstrual fluid, and allowed to incubate at 37.5° C. for sixteen to eighteen hours. However, coagulation did not occur in any instance. Since the possibility exists that the conversion of prothrombin may not occur because of an inhibitor of the reaction between prothrombin, thromboplastin, and calcium, 0.1 ml. and 0.2 ml. menstrual fluid was added to 0.1 ml. oxalated blood plasma, together with 0.1 ml. calcium and 0.1 ml. thromboplastin, and the mixture allowed to incubate. Clotting occurred in the five instances thus studied; the clotting time being the same as in the controls. This obviates the possibility that a prothrombin or thromboplastin inhibitor is present in menstrual fluid.

The fact that menstrual fluid is free of inhibitors of thrombin and thromboplastic activity makes it quite improbable that an anticoagulant is responsible for the presence of noncoagulated blood in the menstrual discharge.

In two experiments (Table I, Tests 7 and 11), it was noted that whereas coagulation of a mixture of fibrinogen and activated serum was not delayed by the menstrual fluid, after incubation for six to eight hours at 37.5° C., the tubes containing menstrual fluid showed a soft gelatinous, semiformed clot, in contrast to the clots

which did not contain menstrual blood. In three experiments, when the menstrual fluid was added to oxalated plasma together with calcium and thromboplastin, the clot that formed was found to have undergone lysis after incubation for sixteen to eighteen hours.

DISCUSSION

Almost all investigators accept the basic facts that normal blood plasma contains a substance, prothrombin, which is activated in the presence of calcium and thromboplastin to form an active coagulant, thrombin. Thrombin then reacts with fibrinogen to form the actual clot, fibrin. It is obvious that the absence of any one of these factors will result in noncoagulability of the blood. Likewise, the presence of any inhibitor (anticoagulant) will prevent the formation of a clot.

By means of some of the modern procedures employed in studies on blood coagulation, we have been unable to detect the presence of prothrombin, thrombin, fibrinogen, or anticoagulants in normal menstrual discharge. These findings apparently are in accord with the hypothesis advocated by various investigators that menstrual fluid is deficient in one or more factors essential for the coagulation of blood. Especially pertinent in this regard are the observations of Bell,[16] King,[17] and Dogliotti,[3] who, with crude and more indirect procedures, obtained data which are essentially similar to those discussed above.

The observation that practically all the factors essential for blood coagulation other than thromboplastin[3] and calcium[22] are absent in the menstrual fluid raises some interesting speculations. It can be assumed that these factors are missing because some mechanism exists which permits the endometrium to impair their passage from the circulating blood into the uterine cavity. However, the observations of Shaw[10] and others that clots can occasionally be found free in the uterine cavity suggests that an impermeability to prothrombin and other factors essential to blood coagulation need not necessarily exist.

Another mechanism which can account for the absence of blood coagulating factors in menstrual fluid would be one involving the utilization of these substances. That is, if the blood leaving the endometrium coagulated in a normal manner and subsequently underwent autolysis, prothrombin and all of the thrombin and fibrinogen would disappear from the menstrual discharge. The fact that clots can occasionally be found in the uterine cavity is in accord with such a point of view, as are the studies of numerous investigators who present evidence for the existence of lytic substances in menstrual fluid. The observation of an increased titer of tryptic enzymes in the circulating blood during the menstrual period[7] may be of some import in this connection. Likewise, in accord with this concept is our observation that a fibrin clot may occasionally undergo lysis when incubated with menstrual fluid. This hypothesis can account for all the observed facts relative to the fluidity and chemistry of the menstrual fluid. Thus, in cases where the bleeding from the endometrium is excessive, the rate of lysis may not be sufficiently rapid to disintegrate all the coagulated blood, and hence numerous clots may be expelled as has been frequently observed. This concept also may account for the conflicting observations of different

investigators, since the presence or absence of various factors essential to blood coagulation would be dependent upon the rapidity of bleeding, the rate of disintegration of the blood clot, and the rate of destruction of the lytic agents.

SUMMARY

Menstrual fluid does not contain detectable amounts of fibrinogen, prothrombin, thrombin, or anticoagulants.

The significance of these findings is discussed, and it is suggested that the blood leaving the endometrium may clot, and that the clot subsequently undergoes digestion by some hypothetical lytic agent. When bleeding is excessive, the rate of lysis may be relatively slow, and undigested clots may be expelled.

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These authors report a case of a 36-year-old colored female, a known syphilitic, with Vincent's cervicitis. The patient complained of abdominal pain for six days. Examination revealed a tender abdomen, slight bloody discharge, a cervix on whose surface craterlike irregularities could be felt. In the speculum the cervix appeared to be markedly ulcerated, the ulcers being covered with a moist, dirty, gray, foul-smelling membrane which would not peel off with ease. Smears and dark-field examinations were positive for Vincent's organisms. Smears and dark-field examinations made from the gums of the patient and her husband were both positive for Vincent's organisms. The cervix was treated with local applications of 2 per cent gentian violet and vaginal instillations of hydrogen peroxide. After thirty-six hours the inflammation was subsiding. After twelve days gentian violet was discontinued and 2 per cent arsphenamine in glycerin was used in its place. Twenty-one days after admission the cervix appeared normal and smears were negative. The patient was advised to discontinue the use of saliva as a lubricant for intercourse.

EUGENE S. AUER.

FRIEDMAN TEST ON SPINAL FLUID IN CASES OF HYDATIDIFORM MOLE AND PREGNANCY

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THE preoperative diagnosis of hydatidiform mole is often difficult. The use of qualitative and quantitative hormonal studies as an aid in diagnosis has been of some value, but there is need for a more exact method. It was, therefore, deemed advisable to investigate the Friedman test on the spinal fluid in cases of hydatidiform mole and to study its reaction in normal pregnancies, pregnancies complicated by cysts, fibroids, and purulent salpingitis, and in ectopic pregnancies.

Owing to the fact that some of these conditions are rather rare and owing to the further difficulties in getting a large series of cases, this small group is presented as a preliminary report.

The recent literature on this subject is rather meager. Zondek and Mathieu mention the fact that normal pregnancy gives a negative spinal fluid Aschheim-Zondek reaction, while hydatidiform mole and chorioepithelioma yield a positive result. In 1929 Ehrhardt performed Aschheim-Zondek tests on the spinal fluid of 50 patients, including certain diseases of children as well as adults. This series contains 18 cases of pregnancy, essentially those complicated by general infections and toxemias. Four cases of toxemia of pregnancy and 1 case of pregnancy at three months complicated by carcinoma of the cervix gave positive A.P.R. I reactions (follicle reaction). None of his 50 cases gave a positive A.P.R. II or A.P.R. III reaction (corpora hemorrhagica or lutea). In another article, Ehrhardt reports 2 cases of hydatid mole that gave positive Aschheim-Zondek reactions on the spinal fluid. However, we have not been able to find very many case reports with the use of the Friedman test in hydatid moles and pregnancy, and it is in this light that our observations are presented.

A routine spinal tap on every case of pregnancy in order to rule out suspected pathology is not advocated. However, it is felt that this procedure is of sufficient importance to the patient's welfare to warrant its performance on certain indications. In cases where the clinical picture or the quantitative hormonal studies are inconclusive, it is of special value. With this test a definite result can be obtained in forty-eight hours, or less. This saving of time may be of extreme importance in some cases. In cases where spinal anesthesia is to be performed for an operation, 5 to 10 c.c. of spinal fluid can be readily removed for examination without danger. This has been done in a number of our cases. In ambulatory patients, spinal puncture may be difficult, but can usually be managed. It has even been done in the patient's home, but this is not to be encouraged.

In this preliminary report, an attempt to demonstrate that the spinal fluid Friedman test is negative in pregnancies which are normal or complicated has been made. So far in our series it has been positive only in cases of hydatid mole. A positive spinal fluid Friedman test

was also obtained in a case of seminoma occurring in a male with an ectopic testicle (proved by operation and autopsy). Our series of cases is rather small, but we hope to add to this group in the near future.

The technique used in performing this test is quite simple. Five to 10 c.c. of spinal fluid, preferably 10 c.c., was injected into the vein of the ear of a virgin rabbit, weighing about 1,600 Gm. No preparation of the cerebrospinal fluid was carried out. In forty-eight hours, the animal was sacrificed (intravenous injection of air was utilized for this purpose). The ovaries were then examined for A.P.R. II and III reactions. Unusually large A.P.R. I reactions were interpreted as negative, but repetition of test was found advisable in these cases. In our series this test was found to be negative in all the cases of normal pregnancy, pregnancy complicated by cysts, tumors, infections, and ectopic pregnancy. It was positive in cases of hydatid mole. The exact mechanism to explain these phenomena is unknown. The reason why the spinal fluid in cases of hydatid mole and chorioepithelioma contains sufficient anterior pituitarylike hormone to give a positive test, and other forms of pregnancy do not, is at present under investigation by us. We do know, however, as is exemplified in Case S. M. that in hydatid mole the Friedman test in the urine may be weakly positive and the prolan A and B titers moderately low and still the spinal fluid Friedman test strongly positive. Subsequent findings corroborated the specificity of the spinal fluid Friedman test in this case, and it was upon the basis of the latter that proper treatment was instituted early.

In this work, it was important to confirm the fact that normal pregnancy, ectopic pregnancy, and pregnancies complicated by cysts, tumors, or inflammation gave negative spinal fluid Friedman tests and that both early and advanced pregnancies also gave negative results. Urinary Friedman tests, findings at operations or subsequent parturition were used as checks upon these observations. To illustrate these facts, the following brief case histories are presented:

CASE 1.—S. M., aged 48 years, gravida ii, para i, was admitted to Beth Israel Hospital on Dec. 7, 1939. Her last menstrual period was Aug. 10, 1939. She "spotted" on September 10 and 11 and also on October 5 and November 15. From November 15 to December 7 (time of admission), there was continuous slight bleeding. Physical examination on admission was negative except for the uterus which seemed slightly larger than should be expected for the period of amenorrhea. The fetal heart sounds were not heard, nor were the fetal parts felt. Friedman test on the urine, done December 8, was reported weakly positive. The spinal fluid Friedman test, done on December 9, was strongly positive. Quantitative A.P.R. III was reported as 8,000 M.U. per liter. On December 12, because of the positive spinal fluid Friedman test, despite weakly positive urinary Friedman test and only 8,000 M.U. A.P.R. III in the twenty-four-hour urine specimen, the uterine cavity was explored digitally and a hydatid mole was expressed.

CASE 2.—R. M., aged 30 years, para ii, gravida iv, was admitted to Beth Israel Hospital January 10, with chief complaint of vaginal bleeding of one week's duration. Her last menstrual period was Oct. 1, 1940. The uterus was about the size of a six to eight weeks' gestation, and she had tenderness in the right lower quadrant. A urinary Friedman test, performed on January 9, was strongly positive. The uterus was curetted on January 11, and the pathologist reported the presence of hydatid mole. Spinal fluid Friedman test done on the fourth postoperative day was positive. Spinal fluid and urine Friedman tests done eight weeks later, on March 7, were negative. At the time of writing, the patient is well and has not been bleeding.

CASE 3.—I. J., a 25-year-old female, gravida ii, para i, was admitted to Beth Israel Hospital on May 2, 1940. On March 31, 1940, a dilatation and curettage was done for uterine bleeding, and hydatid mole was found. The patient was well

until April 25, when she began to bleed profusely. The uterus was only slightly enlarged and our impression was that we were dealing with a profuse menstrual bleeding. On May 6, 1940, the Friedman test on the urine as well as the Friedman test on the spinal fluid was negative. Because of these negative findings and the cessation of bleeding, the patient was discharged on May 6, 1940. She was readmitted on May 31, with a history of staining since her discharge from the hospital on May 6. The urine and spinal fluid Friedman tests were again negative (June 1). Nevertheless, she was curetted and remnants of placenta were found. No evidence of hydatid mole was present. She has been under observation for six months and has remained well.

CASE 4.—S. F., an 18-year-old female, para 0, gravida i, was admitted on March 23, 1939. Her last menstrual period was Dec. 10, 1938. She "spotted" on-and-off, from Jan. 10, 1940, to March 23, 1940. Physical examination revealed a uterus of four months' gravidity, soft and boggy, with a closed cervix. On March 30 a Friedman test on the urine was positive and a test on the spinal fluid was negative (10 c.c.). On June 30, 1939, the patient was seen in the follow-up clinic. The uterus was enlarged to the size of a seven months' gestation, and the fetal heart sounds were heard.

CASE 5.—R. M., aged 43 years, gravida iv, para iv, was admitted on April 1, 1940, for a therapeutic abortion. Her last menstrual period was on Jan. 8, 1940. The uterus was the size of a three months' gestation. On March 8 the Friedman test on the urine was positive. On April 3, the Friedman test on the spinal fluid (5 c.c.) was negative. On April 3 a fundectomy was performed. A fetus 7 cm. long was found.

CASE 6.—E. K., 29-year-old female, para i, gravida ii, was admitted to the hospital on March 27, 1940. Her last menstrual period was on Feb. 25, 1940. She complained of severe pain in the lower abdomen. There was no history of bleeding. The uterus was only slightly enlarged. She was only four days past her expected period. On April 1, 1940, a Friedman test on the urine was positive. On April 1, 1940, the Friedman test on the spinal fluid was negative. After one week's rest in bed, the patient was discharged. She was seen in the follow-up clinic in July, 1940, and the uterus was the size of a four months' gestation. In September, 1940, the uterus was the size of a six months' gestation. The fetal heart sounds were heard.

CASE 7.—A. M., a 32-year-old female, gravida ii, para i, was admitted to the hospital on April 16, 1940. Her last menstrual period was on Dec. 25, 1939. She "spotted" on Feb. 1, 1940, and continued to do so for one week. She was well again until four weeks prior to admission, at which time, the "spotting" returned and continued until the time of admission. On admission, the uterus reached the umbilicus. This was larger than the period of amenorrhea would indicate. Hydatid mole was suspected. On April 19, 1940, the Friedman test on the urine was weakly positive. On April 19, 1940, the Friedman test on the spinal fluid (5 c.c.) was negative. On April 19, 1940, a normal fetus and placenta were delivered spontaneously (four months' size fetus).

CASE 8.—M. L., a 37-year-old female, gravida iii, para ii, was admitted to the hospital on April 22, 1940. Her last menstrual period was on March 8, 1940. Her chief complaint was pain in the lower abdomen. No bleeding was present. She was sixteen days past her expected period. The uterus was irregularly enlarged to the size of a twelve weeks' gestation. The right kidney was ptosed. On April 25, 1940, the Friedman test on the urine was positive. On April 26, 1940, the Friedman test on the spinal fluid was negative. On April 26, 1940, a supravaginal hysterectomy was performed. The pathologic report was "myomatous uterus with early pregnancy."

CASE 9.—H. T., a 23-year-old female, gravida i, was admitted on May 6, 1940. Her last menstrual period was on Jan. 23, 1940. The patient had skipped her February and March periods, but on April 5, she began to bleed continuously

until the date of her admission on May 6, 1940. The uterus was enlarged and a cystic mass was felt in the right adnexal region. A diagnosis of ovarian cyst complicating pregnancy was made. May 9 both urinary and spinal-fluid Friedman tests were negative. At operation, a right ovarian cyst and purulent salpingitis were found. There was no evidence of pregnancy.

CASE 10.—F. D., a 35-year-old female, gravida i, para i, was admitted to the hospital on Sept. 23, 1940. Her history was typical of an ectopic gestation and this diagnosis was made preoperatively. On September 26, the Friedman test on the urine was positive. On September 27, the Friedman test on the spinal fluid was negative. The patient was operated upon on September 28 and an ectopic pregnancy (eight weeks) was found in the left Fallopian tube.

DISCUSSION

Two cases of hydatid mole with positive Friedman tests on the spinal fluid were described. Another case of hydatid mole that had been curetted and practically cured except for a small piece of retained placenta was reported. In this case, the Friedman test on the spinal fluid was negative; subsequent findings and follow-up corroborated the absence of hydatid mole. Case 10 demonstrated that the spinal fluid Friedman test is negative in ectopic gestation. Pregnancy cases in which amenorrhea ranged from four days to six months were presented. The course of events in these cases showed no evidences of hydatid mole or chorioepithelioma, and all gave negative spinal fluid Friedman reactions but positive urinary Friedman tests. In a case of suspected pregnancy (amenorrhea of two months), both urine and spinal fluid Friedman tests were negative. This patient had an ovarian cyst and "pus tubes." Neither of these two conditions had any influence on the spinal fluid Friedman test. Case 8 turned out to be a myomatous uterus with pregnancy; the spinal fluid Friedman reaction was negative, indicative of the fact that fibroids do not influence this reaction.

SUMMARY

1. The Friedman test on the spinal fluid was positive in two cases of hydatid mole and negative in a cured case of hydatid mole.

2. This test was negative in one case of ectopic pregnancy.

3. Normal pregnancy, both early and late, yielded a negative spinal fluid Friedman test.

4. The spinal fluid Friedman test was uninfluenced by myomas or ovarian cysts complicating pregnancy.

5. Cases of ovarian cyst or "pus tubes" with amenorrhea and without pregnancy gave negative spinal fluid Friedman test.

6. One case of seminoma in a male gave a positive spinal fluid Friedman test.

7. The findings in this small series of cases are presented as a preliminary report.

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INOCULATIONS OF INTESTINAL AND VAGINAL TRICHOMONADS INTO THE HUMAN VAGINA

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THE opinion is widespread, particularly among clinicians, that the vaginal and intestinal trichomonads are identical organisms, their apparent differences resulting from conditioning factors of their respective environments. This opinion has considerably influenced the treatment of vaginal trichomoniasis with regard to prophylaxis and the prevention of reinfection. On the other hand, certain laboratory and clinical evidence has been presented which indicates that *Trichomonas vaginalis* and the intestinal trichomonad, *Trichomonas hominis*, are distinct species. The establishment of the validity of either theory is essential to the proper understanding and management of the clinical condition, trichomonas vaginitis.

The studies herein reported are an attempt to approach this problem directly, by the inoculation under similar conditions, of both the vaginal and intestinal trichomonads into the vaginas of human subjects.

Three groups of experiments were conducted.

1. *Trichomonas hominis* was implanted into trichomonas-free vaginas.
2. *Trichomonas hominis* was implanted into vaginas harboring *Trichomonas vaginalis.*
3. *Trichomonas vaginalis* was implanted into trichomonas-free vaginas.

MATERIAL AND METHODS

The subjects for these experiments were volunteers, previously discharged from the postnatal clinic of the Department of Obstetrics of Jefferson Medical College Hospital.

A total of 50 patients was selected for these experiments, forty of whom were within the three-month postnatal period. Twenty-five were trichomonas-free, while 25 harbored *T. vaginalis.*

These patients were first thoroughly studied with regard to abnormalities of the lower genital tract. They were instructed not to douche and to stop all other local treatment. After several days they were questioned concerning local symptoms. At this time, the lower genital tract was exposed with a speculum and examined with particular reference to the condition of the vaginal mucosa and the cervix, as well as the amount and character of the discharge. Gram-stained smears were prepared from the vaginal secretion, and the bacterial flora subsequently graded according to Schröder's classification.[1] The pH of the vagina and external cervical os were determined by the glass electrode method. In the vagina, three sites were chosen: the midvagina, the anterior fornix, and the posterior fornix. The vaginal material was then examined for the presence of trichomonas, by the use of the fresh wet smear and by culture. This procedure was repeated on each visit preceding the inoculations and on every subsequent visit throughout the period of observation.

Trichomonads were then inoculated into the vagina, by the introduction of approximately 1 c.c. of material from the richest part of a forty-eight- to seventy-two-hour culture of *Trichomonas hominis*.[2] Four strains were used. Ten individuals of the trichomonas-free group, in whom *T. hominis* had failed to survive, were also directly inoculated with approximately 1 c.c. of discharge from a trichomonas-positive donor.

Other data, including experiments relating to the viability of the trichomonads used for the inoculations, have been reported elsewhere.[2]

RESULTS

Group 1.—

In the experiments in this group an attempt was made to establish an infestation of *Trichomonas hominis* in 25 *T. vaginalis*-free patients.

Clinical Status Before Inoculation.—A fairly diverse series of patients was represented in this group. Five were entirely symptom free, 16 noticed a slight discharge, and 3 complained of a moderate amount of leucorrhea. One patient, having a rather profuse flow, was found infected with monilia.

On examination, the following findings were noted: The discharge was entirely normal in 7 patients. In 10, the discharge was slight in amount, thin in consistency, and mucopurulent in character. In 7 others, with a mucopurulent discharge, it was moderate in amount in 4, and profuse in 3. The characteristic cheesy type of discharge was noted in the patient with monilia.

The vaginal mucosa was normal in 20 patients, slightly reddened in 3, and showed a marked irritation in 2. The cervix was normal in 10 patients, in 7 there was a slight erosion, and in 8 the erosion was of a moderate degree.

The pH determinations of the vagina and external cervical os are given in Table I, along with the types of bacterial flora.

Clinical Status Following Inoculation.—Repeated inoculations of *Trichomonas hominis* resulted in the production of some symptoms and signs of vaginal irritation in a number of patients, despite the fact that all remained negative for trichomonas throughout. The distribution of the various signs and symptoms were as follows: Five remained entirely free of symptoms, and 5 noticed an increase in discharge, which was quite marked in 1 patient. In 4, a profuse, thin, mucopurulent discharge occurred. Slight vaginal inflammation resulted in 6 instances, while in 8 patients the inflammatory reaction was more marked. Little or no change occurred in regard

TABLE I. T. VAGINALIS-FREE PATIENTS

BACTERIAL FLORA		pH		NO. OF INOCULATIONS	RESULTS		DAYS OBSERVED AFTER INOCULATION
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48-72-HOUR CULTURE	SMEAR	CULTURE	
I	2	4.4-5.0	6.5-6.8	2-3	Neg.	Neg.	35- 70 (2 Patients)
II	4	4.1-5.3	6.4-7.2	3	Neg.	Neg.	12- 35 (2 Patients)
							94-203 (2 Patients)
III	14*	5.2-6.4	6.0-8.0	3	Neg.	Neg.	18- 26 (3 Patients)
							30- 44 (4 Patients)
							70-133 (3 Patients)
Not known	5	4.4-6.1	6.8-7.5	3	Neg.	Neg.	59 (1 Patient)
							112-124 (2 Patients)
							297-313 (2 Patients)

*Four patients failed to return for check-up.

to the cervix, nor did any significant shift in pH occur. The occurrence of signs and symptoms of vaginal inflammation was attributed to the metabolic products of the bacteria and flagellates present in the cultures.

Group 2.—

In this group an attempt was made to transfer *T. hominis* to an environment suitable to the growth of trichomonas, as indicated by the presence of *T. vaginalis* in the vagina. Twenty-five trichomonas-positive patients were used.

Clinical Status Before Inoculation.—Three patients were symptom-free, despite the presence of *T. vaginalis.* Ten noticed a slight discharge, 8 a moderate amount, and 4 complained of a profuse discharge. In the last group, 3 also suffered from pruritus.

The discharge was thick and white in 1 instance, thin and mucopurulent in 17, slight in 5, and of moderate quantity in 12. Seven patients had the characteristic profuse, bubbly, mucopurulent, or grayish discharge.

Irritation of the vaginal mucosa was observed in 14 of these patients, 2 of whom showed "flea-bitten" areas. In 3, the vagina was only slightly inflamed, and in 8 it appeared grossly normal. The cervix was eroded in 21 patients, the degree being classified as slight in 4, and moderate in 17.

In Table II is given the range of vaginal and cervical pH readings, correlated with the type of bacterial flora.

TABLE II. T. VAGINALIS-POSITIVE PATIENTS

BACTERIAL FLORA		pH		NO. OF INOCULATIONS	RESULTS	DAYS OBSERVED AFTER INOCULATION
GRADE	NO.	VAGINAL	EXTERNAL CERVICAL OS	48-72-HOUR CULTURE	CULTURE	
I	0	–	–	–	–	–
II	2	4.9-5.9	6.8-7.0	3	Neg.	12- 26 (2 Patients)
III	20*	5.3-6.1	6.0-8.0	3	Neg.	7- 16 (6 Patients) 26- 54 (7 Patients) 77-80 (2 Patients) 247-281 (2 Patients)
Not known	3	5.2-6.0	7.5-7.9	3	Neg.	19- 28 (2 Patients) 77 (1 Patient)

*Three patients failed to return for check-up.

Clinical Status Following Inoculation.—Culture studies made throughout the period of observation subsequent to the inoculations revealed that all patients remained free of *T. hominis,* though continuing to harbor *T. vaginalis* in large numbers. In this group no significant change in symptoms or signs occurred following inoculation.

The 4 strains of *T. hominis* employed in the experiments of Groups 1 and 2 were established experimentally in the intestine of kittens.[2]

Group 3.—

It was also desired to determine whether or not *T. vaginalis* could be successfully implanted in vaginas refusing to tolerate *T. hominis.* Consequently, 10 trichomonas-free patients in whom *T. hominis* inoculations were unsuccessful, were submitted to one direct *T. vaginalis* inoculation from freshly collected discharge. Three separate donors were used in these experiments.

Secretion was collected on a swab from the positive patient and mixed thoroughly with 2 to 3 c.c. of physiologic saline solution. Approximately 1 c.c. of this material was used to swab the posterior portion of the vagina of the negative patient.

Clinical Status Following Inoculation.—The various clinical and laboratory findings in these patients previous to, and following, the inoculations are given in Table III.

Trichomonas vaginalis infestation was produced in 8 patients, who remained positive for the flagellates over varying periods of time (Table III). Three of the inoculated subjects showed trichomonas at seven days, and 4 showed them within three weeks. The eighth, who may have acquired her flagellates elsewhere, remained negative until the thirty-fifth week. Two other recipients remained consistently negative over periods of four and nine weeks, respectively.

TABLE III. PATIENTS INOCULATED WITH T. VAGINALIS FOLLOWING UNSUCCESSFUL T. HOMINIS IMPLANTATIONS

PATIENT	SYMPTOMS			SIGNS				pH		BACT. FLORA	NO. DAYS OBSERVED BEFORE INOC.	DAY PATIENT OBSERVED POSITIVE	NO. DAYS PATIENT POSITIVE
	DISCHARGE	PRURITUS	BURNING	AM'T DISCH.	TYPE	VAG. INFL.	CERVICAL EROSION	VAG.	CERV. OS	GRADE			
1. Before	+	–	–	+	thin white	–	+	5.6-6.1	7.5	III	21	7	40
After	–	–	–	+	m.pur.* bubbly	–	+	5.0-5.3	7.1	III			
2. Before	+	–	–	+	thick white	–	+++	4.4-4.7	7.2	II	26	7	82
After	++++	–	–	++++	thin m.pur.	+	++++	4.1-4.4	7.3	II Monilia			
3. Before	–	–	–	++	m.pur. bubbly	–	–	4.9-5.4	5.9 (Dis.)	III	16	19	19
After	+	+	+	+++	m.pur. bubbly	++	++	6.2-6.4	6.6	III		Menstruating	
4. Before	+	++	–	++++	m.pur. cheesy	++++	++++	4.4-5.6	5.0 (Dis.)	III Monilia	21	7	91
After	++	+++	–	++++	m.pur. cheesy	++++	++++	4.4-5.5	6.4	III Monilia			
5. Before	+	–	–	++	thin white	–	–	4.1-4.6	6.4	II	167	Negative	
After	+	–	–	+	white bubbly	+	+	5.2-6.0	6.9	II		28	28
6. Before	++	–	–	+++	white mucoid	–	+	4.4-5.0	6.5	I	43	19	28
After	+++	–	–	+++	thin m.pur. bubbly	+	++ (hemor.)	5.2-5.5	7.2	II			
7. Before	+	–	–	+	thin white	+	+	4.2-4.7	6.5	II	21	16	16
After	+	–	–	+	thin white	+	+	4.4-5.5	7.6	II			
8. Before	–	–	–	+	thick white	–	–	4.8-5.1	7.5	III	118	21	49
After	+	+	–	++	m.pur. cheesy	++	–	4.4-4.8	7.4	III Monilia			
9. Before	+	–	–	+	white mucoid	+	+	4.6-4.9	6.9		128	250	250
After	+	–	–	+	thin m.pur.	+	+	4.7-5.4	7.0				
10. Before	+	–	–	+	thin m.pur.	–	–	4.6-5.3	6.5	III	12	Negative	
After	+	–	–	+	thin m.pur.	–	+	5.1-5.4	7.5	III		61	61

*m.pur., mucopurulent.

Subsequent to direct inoculation, symptoms and signs became aggravated in 2 patients (Cases 3 and 6). In 3 (Cases 1, 6, and 9), the discharge became mucopurulent, being also bubbly in character in Patients 1, 5, and 6. In Cases 6, small hemorrhagic spots, so-called "flea-bitten" areas, appeared on the vaginal cervix. Monilia was inadvertently transferred to two patients (Cases 2 and 8); an acute exacerbation of symptoms followed.

SUMMARY

1. Twenty-one *T. vaginalis*-free patients remained negative after repeated intravaginal inoculations from cultures of *T. hominis.*

2. Twenty-two patients positive for *T. vaginalis* remained likewise negative for *T. hominis* after similar inoculations.

3. *T. vaginalis* was easily transferred to a series of negative women by direct inoculations of positive vaginal secretion.

4. It is concluded that contamination from the rectum is not a method of acquiring vaginal trichomoniasis.

5. These experiments also support the opinion that *T. vaginalis* and *T. hominis* are separate and distinct species.

CONCLUSIONS

The evidence which has been presented in these experiments indicates that the intestinal trichomonad, *T. hominis,* is unable to establish itself in the human vagina, even under conditions which are favorable to *T. vaginalis.*

Such results are of considerable clinical significance in that they indicate that contamination from the rectum is not a means by which vaginal trichomoniasis is acquired, as previously claimed.[3] The results also constitute further evidence of specific difference between *T. hominis* and *T. vaginalis.*

The facile implantation of *T. vaginalis* from one patient to another, as shown here, is important, especially in view of the reported difficulty of producing similar infestations from pure cultures of the organism.[4]

The characteristic symptoms and signs, frequently described as those of a trichomonas vaginitis, developed in only two patients after direct transmission. Others have reported a higher incidence in the occurrence of these characteristic manifestations.[5]

We are grateful to Dr. Norris W. Vaux for his interest and the facilities of his department, and to Dr. D. H. Wenrich for his helpful advice and criticism.

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THE CONTRACTILE RESPONSE OF THE UTERUS TO POSTERIOR PITUITARY EXTRACT DURING LATE PREGNANCY AND ITS RELATION TO THE DURATION OF LABOR

A Study of 26 Primigravidas With the Lóránd Tocograph

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WHILE studying the activity of the uterus which takes place during late pregnancy, posterior pituitary extract was administered to a series of patients in order to determine the character of the contractile response which the uterus might exhibit at that time.

Some individuals responded and others did not. It was possible to classify the positive responses in several categories, depending upon whether the reaction was purely clonic, or had a tendency toward tetany; and if the latter condition occurred, whether or not the spasm interfered with the registering of the clonic contractions.

This variation in response to the drug, and the well-known variation in uterine activity observed at the time of labor, suggested that there might be a correlation between the two. Would the patient whose uterus failed to respond to posterior pituitary extract before labor be less sensitive to the stimulus of labor than one whose uterus did react? And would there be a significant relation between the character of any positive responses during pregnancy, and the kind of contractions observed during labor? The present study attempts to throw light upon these questions.

MATERIALS AND METHODS

The records of uterine activity were made between June 30, 1939, and July 9, 1940, upon 26 women, pregnant for the first time, and residing in the Sheltering Arms Home, Philadelphia. The observations were recorded with the latest model Lóránd tocograph.[1]

Each patient rested upon her bed for ten minutes before the recording was begun. After a fifteen-minute control period of recording, and without removing the tocograph, she received an intramuscular injection of posterior pituitary extract (obstetric pituitrin, Parke Davis & Co.) in the upper arm. The tocographic record was continued for a period of thirty minutes following the injection. The pituitrin was assayed at 10 international units per cubic centimeter of solution.

The majority of the patients were delivered in the Hospital of the University of Pennsylvania. The study was limited to primigravidas who exhibited no evidence of cephalopelvic disproportion; ones who were delivered vaginally and whose infants at birth weighed between 2,500 and 4,000 Gm. The average age of the women was 20 ± 4.2 years. Their uterine activity was recorded on an average of 19 ± 5.7 days before labor. Each individual supplied only a single record for the present analysis.

TABLE I. THE CONTRACTILE RESPONSE OF THE PREGNANT UTERUS TO POSTERIOR PITUITARY EXTRACT IN RELATION TO THE DURATION OF LABOR

RESPONSE	PATIENTS									
			MINIMS OF EXTRACT							
			1		1.5		2		3	
	NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.	PATIENTS NO.	MEAN DURATION OF LABOR HR.
No	7	21.3 ± 9.6	2	24.5	1	10.0	2	29.2	2	15.6
Yes	19	9.3 ± 5.4	4	11.9	4	6.8	5	10.0	6	8.5
Clonic	11	6.9 ± 4.8	1	1.8	3	4.8	4	13.0	3	7.2
Tetanic	8	12.5 ± 4.6	3	15.3	1	13.0	1	11.0	3	9.9
Incomplete	7	11.2 ± 3.3	2	12.3	1	13.0	1	11.0	3	9.9
Complete	1	21.5 ± 0.0	1	21.5	0	–	0	–	0	–

Recording the influence of the character of the contractile response of the uterus to posterior pituitary extract, nineteen days before labor, upon the duration of labor. Observations upon 26 primigravidas, arranged according to the amount of extract employed. Note: (a) Shortness of labor of patients experiencing a response, compared with length of labor of those who had none; (b) shortness of labor of women exhibiting a clonic reaction, compared with ones having a tetanic response.

RESULTS

The incidence of responses and the character of the positive ones are summarized in Table I, and arranged according to dosage, where they are correlated with the duration of labor.

Positive responses are classified as: (a) Clonic, (b) incomplete tetanic, and (c) complete tetanic.[2]

A *clonic* response is characterized by a series of rhythmically recurring contractions, not associated with any increase in the tension of the uterus.

An *incomplete* tetanic response is characterized by clonic contractions associated with an increase in the tension of the uterus, which is indicated by an elevation of the valleys between the waves. The increase in tension in this instance, however, does not prevent the registration of any of the clonic contractions.

A *complete* tetanic contraction is characterized by the presence of clonic contractions, associated with an increase in tension which blocks out one or more of the clonic contractions.

Correlation of the mean duration of labor of all patients irrespective of the amount of posterior pituitary extract which they received, with the character of their responses, Columns 1 and 2, Table I, indicates that the women, experiencing no response had significantly longer labors than those who gave a response. The difference in the length of the labors in the two groups was twelve hours, with a standard error of 3.9 hours.

The patients experiencing any tetanic tendency whatever had labors of a mean duration of 12.5 hours, whereas those having an uncomplicated clonic reaction, had a mean duration of only 6.9 hours. The difference is 5.6 hours, with a standard error of 2.2 hours. Since this difference is nearly three times its standard error, for practical purposes, it might be considered statistically significant.

It is of interest, if not statistically significant, that the mean duration of labor of the 7 patients experiencing an incomplete tetanic response, was shorter than that of the one patient having a complete tetanic reaction.

DISCUSSION

The present series of observations, admittedly, is small, but this disadvantage is offset, to a certain extent at least, by the uniformity of the material.

In a previous communication,[2] we have indicated the roles played by individual variability, parity, the duration of pregnancy, the presence of labor and other factors, which influence the contractile response of the pregnant uterus to oxytocic drugs.

The present patients were all primigravidas; they were close to the same age, and lived under uniform conditions during the period covered by the study. Another advantage in utilizing this group lies in the fact that the majority of the patients were delivered under our own supervision, which made it possible to secure uniform and satisfactory records of the character and duration of their labors.

The question may be raised as to the suitability of the duration of labor as a measure of the efficiency of the uterine contractions at that time. The answer is that we were unable to find any other more practical measuring rod.

The doses of posterior pituitary extract employed in the present study varied from 1 to 3 minims. These amounts produced a sensation of abdominal constriction in 9 instances, and a feeling of pain in one case. No other untoward effects were noted.

Both the incidence and degree of subjective sensation, resulting from the administration of posterior pituitary extract during pregnancy,

vary with the duration of pregnancy. Of 63 treatments administered at weekly intervals to the present 26 patients, and to 6 additional ones, prior to the thirty-second week of gestation, the dose in no instance exceeding 3 minims, only 6 (9.5 per cent) were followed by any sensation of abdominal constriction and none by any pain. On the other hand, of 223 treatments given to the same patients after the thirty-first week of gestation, 51 (22.8 per cent) resulted in a feeling of tightness and 11 others were followed by a definite sensation of pain. The pain in all instances was mild except in the case of one patient whose uterus was extremely tense throughout pregnancy. Her pain was so severe after the first two tracings that later treatments had to be abandoned.

Another patient, not included in the above group, whose uterus was not tense, experienced a severe and prolonged uterine spasm, on the fourteenth day before labor, following a dose of only 1.5 minims of pitocin (Parke, Davis & Co.).

These observations suggest that the test dose of posterior pituitary extract should be small if painful responses are to be avoided. However, even where we have employed a dose as large as 3 minims no untoward reaction other than pain was noted.

In previous reports it was shown that the pregnant uterus becomes unusually active[3] and reactive[2] to posterior pituitary extract during the week or two immediately prior to the onset of clinical labor. The nineteenth day before labor, therefore, was selected as the time to study the present patients, in order to avoid the later period. A period earlier than the nineteenth day might have served equally well.

In view of the small number of observations, and because the study is limited to primigravidas, it cannot be said that the present inferences necessarily can be applied generally. Nevertheless, the observations do not appear to be illogical, nor do they seem to be out of line with others that we have made thus far. The results are presented for what they may be worth. Undoubtedly it will be necessary to assemble additional data, and rule out the influence of the many variables which influence response, before the relationship between response and the character of the contractions which occur during labor is fully understood, and before the method should be employed clinically for predicting the nature of the impending labor.

SUMMARY AND CONCLUSIONS

1. The uterine activity of a consecutive series of 26 primigravidas was registered with a Lóránd tocograph, approximately nineteen days before the onset of labor, while the patients were receiving intramuscular injections of posterior pituitary extract.

2. The incidence of responses and the character of the positive ones were correlated with the duration of labor.

3. Individuals experiencing a response had significantly shorter labors than those who gave no response.

4. Women having an uncomplicated clonic reaction had significantly shorter labors than those whose responses exhibited a tendency toward tetanic spasm.

5. Seven patients having a mild degree of tetanic reaction had, on the average, shorter labors than one individual who showed a more severe degree of tetanus.

6. From these observations it might be concluded that, under the conditions of this study, there existed a significant relation between the character of the uterine contractile response to posterior pituitary extract administered during late pregnancy and the character of labor as indicated by its length.

The author is indebted to Dr. Dorothy L. Ashton for the privilege of studying the patients on her service at the Sheltering Arms Home.

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A STATISTICAL REPORT OF 1,914 CASES OF HYSTERECTOMY

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ON TWO previous occasions, statistics on hysterectomy have been reported from this department which included all cases up to 1935.[1, 2] This report covers the last five-year period ending Jan. 1, 1940, and comprises 1,914 consecutive cases of hysterectomy. In 1919, W. H. Weir adopted the pan- or total hysterectomy as the procedure of choice, and since then the proportion of this type of operation has steadily increased. The technique[3] is a simplified modification of previously described operations.

As seen in Table I, this operation now constitutes almost 75 per cent of all hysterectomies. The supravaginal hysterectomy is, as a rule, done by the resident staff only when complications are so extensive that panhysterectomy cannot be done with safety. The number of vaginal hysterectomies is low because this procedure is usually reserved for those patients with at least a second-degree prolapse. The proportion of white to colored patients is the same in all groups except in vaginal hysterectomy in which it is interesting to note the very small incidence of this operation in colored people, due to their seldom having prolapse. The majority of parous patients fall into the pan- and vaginal hysterectomy groups, particularly the latter, where prolapse is almost invariably a result of birth trauma. In the supravaginal group, slightly less than one-half are nulliparous. The explanation for this is plain when one realizes that the cervix is more liable to be normal in the nulliparous patient and the frequency of salpingitis in this group with resulting complications makes panhysterectomy difficult in a larger number.

The age distribution of this series is shown in Table II. The majority of cases fall into the fourth and fifth decades of life at, or near, the time of the menopause when symptoms of pelvic lesions may become most

TABLE I. DISTRIBUTION OF CASES

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Distribution								
Resident Staff	81	4.23	119	6.2	905	47.2	1,105	57.7
Visiting Staff	49	2.56	229	11.9	531	27.7	809	42.3
Combined Staffs	130	6.79	348	18.2	1,436	74.9	1,914	100.0
Color Distribution								
White	122	93.8	246	70.6	987	68.8	1,355	70.8
Colored	8	6.2	102	29.4	449	31.2	559	29.2
Parity								
Para 0	6	4.6	159	45.6	368	25.6	533	27.8
Para i plus	124	95.4	189	54.4	1,068	74.4	1,381	72.2

marked. It should be noted also that vaginal hysterectomy cases are spread out over the fifth, sixth, and seventh decades of life when the pelvic supports participate in the general tendency of pelvic tissues to thin out and relax. The two total hysterectomies on young girls were done for intractable bleeding in one instance and in the other for pelvic structures hopelessly damaged by pelvic infection.

The incidence of diagnosis shown in Table III illustrates the relative frequency of occurrence of common gynecologic conditions. Chronic cervicitis is purposely omitted, because in the pathologic reports the diagnosis was made in practically every case in which the cervix was

TABLE II. AGE DECADE DISTRIBUTION

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Second decade 10-19					2	0.1	2	0.1
Third decade 20-29	4	3.1	31	8.0	161	11.2	196	10.2
Fourth decade 30-39	31	23.8	145	41.6	638	44.5	814	42.5
Fifth decade 40-49	40	30.7	140	40.2	512	35.7	692	36.1
Sixth decade 50-59	23	17.7	31	8.9	108	7.53	162	8.4
Seventh decade 60-69	28	21.5	1	0.3	15	1.04	44	2.29
Eighth decade 70-79	4	3.07					4	0.20

TABLE III. INCIDENCE OF DIAGNOSIS

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Relaxed vaginal outlet	127	97.8	103	29.6	890	62.0	1,120	58.5
Myoma	33	25.4	242	69.5	788	54.9	1,063	55.6
Salpingitis			127	36.5	356	24.8	483	23.8
Endometriosis	8	6.15	41	11.8	104	7.3	153	7.9
Ovarian tumors			18	5.2	50	3.5	68	3.6
Carcinoma of fundus			5	1.4	21	1.5	26	1.4
Carcinoma of cervix					7	0.49	7	0.36
Prolapse	118	90.8	1	0.3	93	6.5	212	11.0

removed. Relaxed vaginal outlet follows roughly the incidence of childbirth. The higher incidence of salpingitis in the supravaginal hysterectomy group is due to the complications resulting from this condition. The diagnosis of carcinoma of the cervix appears infrequently in this series due to the fact that the majority of these are treated with radium and x-ray. The 7 present were early cases treated by radical hysterectomy for teaching purposes or were undetected before operation. The incidence of prolapse is very high in the vaginal hysterectomy group, because this procedure is rarely performed in this clinic except for this condition.

In attempting to classify the number and types of symptoms for which hysterectomy is done, there is such a variation in number and degree that a true picture cannot be drawn. Table IV, is, therefore, at best only a rough determination from the information supplied by the patient and recorded in the history. Urinary symptoms have been omitted because of their variety and frequency and because they are mostly secondary. It is interesting that the symptoms are the same in the pan- and supravaginal hysterectomies.

Additional operative procedures at the time of hysterectomy are frequently either necessary or desirable. The incidence of these is shown in Table V. A dilatation and curettage is felt to be a diagnostic procedure in this clinic and should be done if necessary some time before the operation is decided upon. As a result, it is not often done as an imme-

TABLE IV. DISTRIBUTION OF MOST COMMON SYMPTOMS

	130 VAGINAL HYSTERECTOMY		348 SUPRAVAGINAL HYSTERECTOMY		1,436 PANHYSTERECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Pain	66	50.7	234	67.2	964	67.1	1,264	66.1
Bleeding	13	10.0	139	40.0	624	42.5	776	40.5
Tumor			40	11.5	163	11.5	203	10.6
Prolapse	83	63.8	4	1.15	16	1.1	103	5.4

TABLE V. ADDITIONAL OPERATIVE PROCEDURES

	130 VAGINAL HYSTERECTOMY		348 SUPRAVAGINAL HYSTERECTOMY		1,436 PANHYSTERECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Dilatation and curettage	1	0.8	65	18.6	79	5.5	146	7.6
Perineorrhaphy	125	96.2	95	27.2	898	62.5	1,118	58.4
Anterior colporrhaphy	83	63.8	18	5.2	257	17.9	358	18.7
Partial removal of adnexa	5	3.8	131	37.6	476	33.2	612	32.0
Complete removal of adnexa			85	24.4	262	18.2	347	18.1
Appendectomy (possible)			194	71.3	928	84.5	1,122	81.1
Hemorrhoidectomy	10	7.7	12	3.4	96	6.7	118	6.2
Cholecystectomy					10	0.7	10	0.5

diate preliminary to hysterectomy. The repair of a relaxed pelvic floor as an additional pelvic support following hysterectomy is felt in this clinic to be essential. Because the posterior relaxations are the most frequent, the perineorrhaphies closely parallel the occurrence of childbirth in these patients. The incidence of appendectomy is high, because it is done routinely except when the condition of the patient or the difficulties in removal of the appendix contraindicate the procedure. Primary disease in the adnexa and incidental pathologic conditions necessitating partial or complete removal of the adnexa are frequently found. Ovaries are always saved when possible. Cholecystectomy in addition to pelvic work was done on ten occasions by one operator, but this combination operation is usually felt to be too hazardous.

Injuries to the ureters, bladder, and bowel are one of the chief worries of the operator. However, consciousness of these dangers has kept the number extremely low as shown in Table VI. It should be noted that the incidence was no greater in the panhysterectomies than in the supravaginal hysterectomies.

The various common postoperative complications are enumerated in Table VII. In spite of the fact that the majority of cases are clean, the number of infected wounds, although not great, is perhaps more than it should be. We hope closer attention to hemostasis and preoperative preparation will help in correcting this. Six of the 11 patients with peritonitis died. None could be attributed to removal of the appendix. Seven of the 15 cases of pulmonary embolus were fatal. The high incidence of cystitis is due to the necessity of traumatizing the bladder somewhat at operation. However, work is now being done on

TABLE VI. OPERATIVE COMPLICATIONS

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
			NO.	%	NO.	%	NO.	%
Cut ureter			1	0.28	3	0.21	4	0.21
Torn bladder			2	0.57	10	0.69	12	0.63
Torn bowel			2	0.57	7	0.48	9	0.47

TABLE VII. POSTOPERATIVE COMPLICATIONS

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Infected wound			14	4.0	53	3.7	67	3.5
Peritonitis			4	1.15	7	0.49	11	0.57
Phlebitis			3	0.86	12	0.84	15	0.78
Fistula					6	0.41	6	0.31
Pulmonary embolus	2	1.54	2	0.57	11	0.77	15	0.78
Pyelitis	4	3.07			13	0.91	17	0.89
Cystitis	27	20.8	23	6.6	107	7.5	157	8.2
Pneumonia	2	1.54	8	2.3	13	0.91	23	1.2
Hemorrhage			3	0.86	11	0.77	14	0.73

better care of the bladder postoperatively to reduce the occurrence of cystitis. It should be noted again that the number of complications is approximately the same in the pan- and supravaginal hysterectomies.

The postoperative morbidity, Table VIII, is determined by the number of days the patient's temperature reaches 38.5° C. or higher. The vaginal hysterectomies show a somewhat higher morbidity. It is also found to be higher in the supravaginal hysterectomies due to the increased number of operative complications in this group.

The mortality rates are shown in Table IX. The 4 deaths in the vaginal hysterectomies give a higher rate than in the other types of hysterectomies. These women were older and also poorer operative risks. The number of vaginal hysterectomy cases, however, is not sufficient to give an accurate mortality rate for this type of operation.

TABLE VIII. MORBIDITY

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Temperature below 38.5° C.	55	42.3	150	43.1	702	48.9	907	47.4
Temperature above 38.5° C. for one day	29	22.3	59	16.9	399	21.5	397	20.7
Temperature above 38.5° C. for more than one day	46	35.4	139	40.0	425	29.6	610	31.9

TABLE IX. MORTALITY RATES

	130 VAGINAL HYSTEREC-TOMY		348 SUPRAVAGINAL HYSTEREC-TOMY		1,436 PANHYSTER-ECTOMY		1,914 TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Resident Staff	2	2.48	7	5.88	10	1.10	19	1.72
Visiting Staff	2	4.08	1	0.43	1	0.188	4	0.49
Combined Staffs	4	3.08	8	2.30	11	0.767	23	1.2

A mortality rate of 5.88 per cent in the resident staff's series of supravaginal hysterectomies is undoubtedly high. However, this procedure is done only when panhysterectomy is found to be too difficult. The group, therefore, includes practically all the complicated cases and a higher rate is to be expected. The visiting staff tend to do more supravaginal hysterectomies proportionally, and their mortality rate of 0.43 per cent is low.

The resident staff did 905 panhysterectomies or slightly less than double the number done by the visiting staff. In this series, there were only 10 deaths, or 1.1 per cent. None of the members of the resident staff, except two who did 37 cases, had more than two years of experience in specialized gynecology. In spite of this inexperience, but because of the standardized and simplified technique, the mortality rate

is very low. With the visiting staff, the results are even more remarkable. In the 531 cases, there was only one death, or a 0.18 per cent mortality. Combining both groups of panhysterectomies, there were 1,436 cases in all with a mortality rate of 0.767 per cent. The total mortality rate in 1,914 cases of all types of hysterectomies is 1.2 per cent.

In conclusion, statistics have been presented and briefly explained on a large number of consecutive hysterectomies, the majority of which were panhysterectomies. The extremely low mortality rate and the absence of increased operative and postoperative complications in the panhysterectomy group leads us to believe that, in properly trained hands, the operation involves no greater risks than the supravaginal hysterectomy and should be the one of choice when the uterus is to be removed.

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TATTOOING WITH MERCURIC SULFIDE FOR THE TREATMENT OF INTRACTABLE PRURITUS VULVAE AND ANI*

An Anatomicoclinical Study

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INTRODUCTION

THERAPEUTIC tattooing with mercury sulfide and other chemicals has been used in the past for a variety of medical and surgical conditions.[1] Recently, this form of therapy has been successfully employed for the treatment of intractable pruritus ani,[2-4] and in selected cases of pruritus of leucoplakia-kraurosis vulvae.[5] Tattooing has proved to be of little value thus far in the treatment of pruritus vulvae of undetermined origin or with superimposed dermatitis. A satisfactory technique of tattooing of the vulva, comparable to that described for the tattooing of the perianal and anal regions[1] is in process of development. Difficulty has been encountered, especially in the tattooing of the clitoris and the surrounding cutaneous folds.

Preliminary investigations of the mechanism of the action of mercury sulfide deposited in the corium by tattooing point to functional impairment of the cutaneous sensory terminals with a resultant alteration in the capacity of this neural system to respond to adequate stimuli. Apparently, a change in the cutaneous modalities is produced which, within limits, is proportional to the amount of intracutaneous deposit of mercury sulfide.[4] The mechanical trauma alone produced by the tattoo-

*Presented, by title, at a meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 5, 1941.

ing machine without deposition of mercury sulfide[4] is ineffectual in producing permanent relief of the pruritus ani.

Although cutaneous syphilitic lesions apparently do not occur in the areas of skin that are tattooed with mercury sulfide,[6-8] convincing proof of the antiseptic value of intracutaneously deposited mercury sulfide in infections other than syphilis is still lacking. This is in agreement with Aoki.[7]

THE PRESENT STUDY

The work embodied in this paper deals with histologic studies of skin which had been tattooed with mercury sulfide as the treatment of intractable localized pruritus; particular reference was made to the fate of mercury sulfide deposited intracutaneously and to its possible effect on the skin.

Fractional skin biopsies were taken from the perineoperianal junction of a woman treated for intractable pruritus perinei and ani immediately after tattooing (Fig. 1, *A*), at three months (Fig. 1, *B*), six months (Fig. 1, *C*), and ten months (Fig. 1, *D*). Fig. 1, *A* shows many perforations in the epidermis by puncture holes with considerable deposit of mercury sulfide in the epithelium and massive deposition in the upper portion of the corium. No other significant changes are observed. Fig. 1, *B* shows a subepithelial deposit of clumps of mercury sulfide; at this stage most of the deposit is in the upper corium, with some of it in the middle portion of the corium. Infiltration of round cells is present without evidence of foreign body giant cell reaction. The epithelium appears normal. This corresponds to the clinical observation that desquamation of the tattooed epidermis occurs within a few days after treatment and that re-epithelization takes place within a few weeks. The histologic pictures seen in Figs. 1, *C* and *D* are essentially the same as that observed in Fig. 1, *B*.

Another patient had the entire vulva tattooed with mercury sulfide because of pruritus of undetermined origin. Six months after tattooing, a biopsy was performed and a specimen for histologic study was removed from the skin of the right side of the mons veneris. A biopsy of the skin of the opposite side of the mons was performed twelve months after tattooing. Like Figs. 1, *B*, *C*, and *D*, these sections show the deposit of clumps of mercury sulfide in the corium without evidence of foreign body giant cell reaction.

The third patient was a 60-year-old white woman, who had the perianal circumference, perineum, and the posterior portions of the labia majora tattooed with mercury sulfide in two stages (Aug. 11, and Sept. 1, 1939) because of intractable pruritus perinei and ani. The left perineoperianal region was incompletely tattooed with resultant skipped areas in which recurrence of mild intermittent pruritus developed. A study of the cutaneous modalities, while unsatisfactory because of the patient's poor cooperation, nevertheless revealed suggestive diminution of the painful and tactile sensations on the opposite perineoperianal side which had been adequately tattooed and which was free from any recurrence of pruritus. Biopsies of skin from each perineoperianal aspect were performed Aug. 16, 1940 (about one year after tattooing). The histologic examination of skin removed from the incompletely tattooed side in which some intermittent pruritus recurred showed areas that had either no mercury sulfide or an uneven scant deposit (Fig. 2, *A*). In contrast, the adequately tattooed skin of the opposite nonpruritic side of the same patient revealed a uniform and abundant subepithelial deposit of mercury sulfide Fig. 2, *B*). Again, no evidence of foreign body giant cell reaction is discernible in these sections.

The fourth patient was tattooed with mercury sulfide because of distressing pruritus vulvae, perinei, and ani caused by leucoplakia-kraurosis; the pruritus had not been controlled by a previous partial vulvectomy and four subsequent surgical procedures.[5] It was noted that "one month after tattooing the skin about the

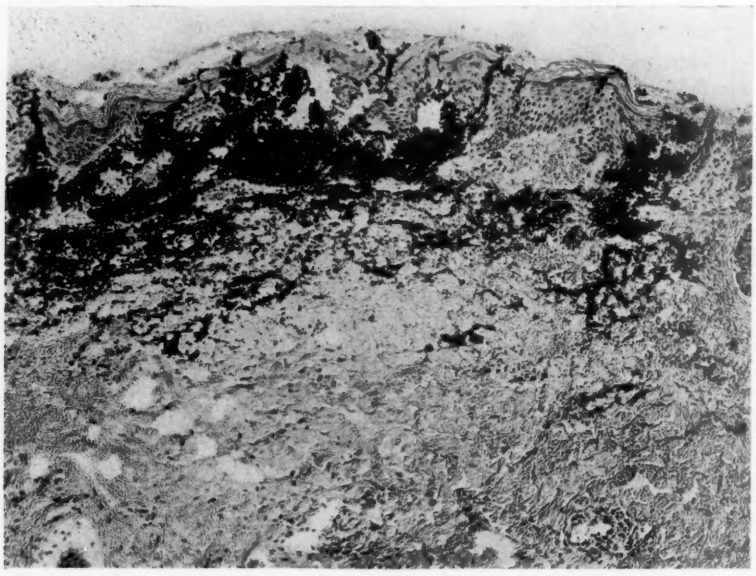


Fig. 1, *A*.

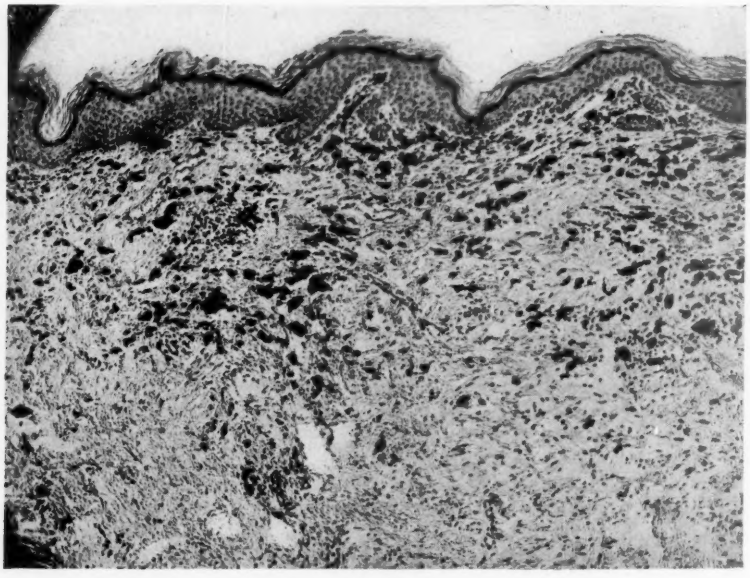


Fig. 1, *B*.

Fig. 1.—Photomicrographs of sections of tattooed perineoperianal skin taken at various intervals of time (Case 1). *A*, Immediately after tattooing, showing perforations in the epidermis with considerable deposit of mercury sulfide in the epithelium and massive deposition in the upper corium. *B*, Three months later, showing a subepithelial deposit of clumps of mercury sulfide without evidence of foreign body giant cell reaction. At this stage most of the deposit of the chemical is in the upper corium with some of it in the middle corium. *C*, Six months after tattooing, showing a histologic picture similar to that of *B*. *D*, Ten months after tattoo, showing a histologic picture essentially the same as that observed in *B* and *C*.

introitus and in the perianal region, with the exception of the perineal area, was normal in appearance.'' Furthermore, eight months later the patient was still free from pruritus ''in spite of the presence of moderate excoriation of the perineum''; this excoriation was believed to be caused by a continuous escape of vaginal discharge for which the patient refused treatment as she preferred to ''leave things well enough alone.'' On July 26, 1940, about thirteen and one-half months later, the patient noted burning and pain in the perineum, especially after defecation. Examination revealed vaginal discharge and a grayish white perineum with three superficial fissures, of which one extended to the anal orifice. One week later, there occurred

Fig. 1, *C*.

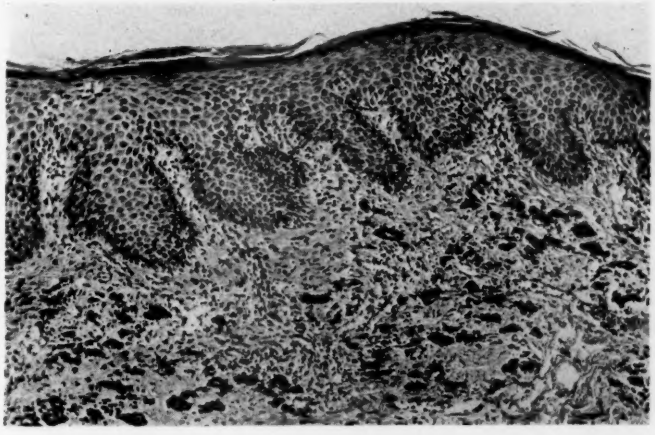
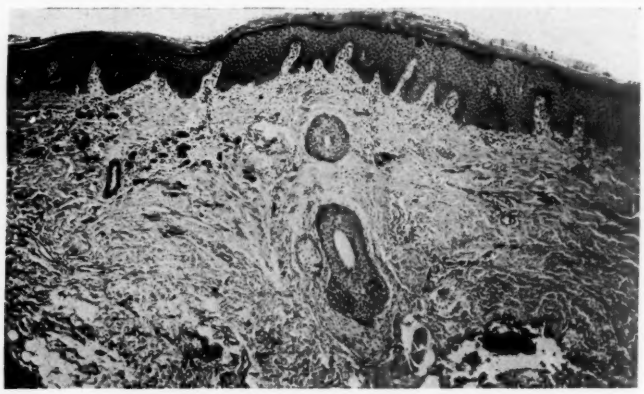


Fig. 1, *D*.

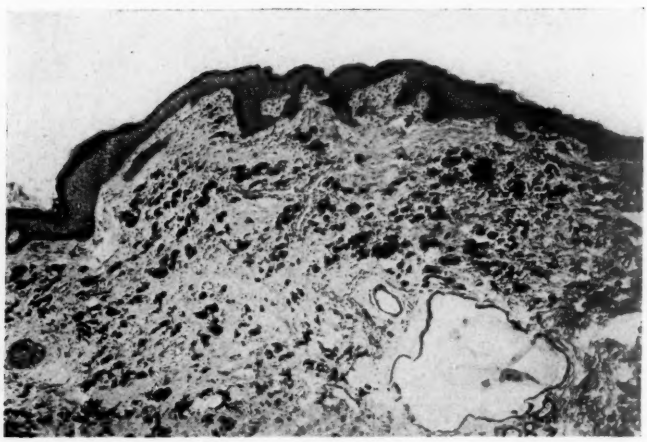
moderate pruritus confined only to the perineum. Biopsies of skin were taken from the perineum and from a well tattooed nonpruritic area, 2 cm. from the site of the perineal biopsy. The histologic examination of the perineum (Fig. 3, *A*) shows a scant deposit of mercury sulfide deep in the corium, many lymphocytes, and leucocytes. The section from a well-tattooed nonpruritic (control) area shows a uniform and an abundant subepithelial deposit of mercury sulfide, as well as moderate infiltration of round cells (Fig. 3, *B*). (The elastica stains of both sections also show fragmentation and degeneration of the elastic fibers.)

COMMENT

The histologic studies of sections of skin taken immediately after tattooing show a homogeneous mass of mercury sulfide chiefly situated in the upper corium with some deposit in the epithelium. Later on, the chemical is localized in the corium and seems to break up into smaller



A.

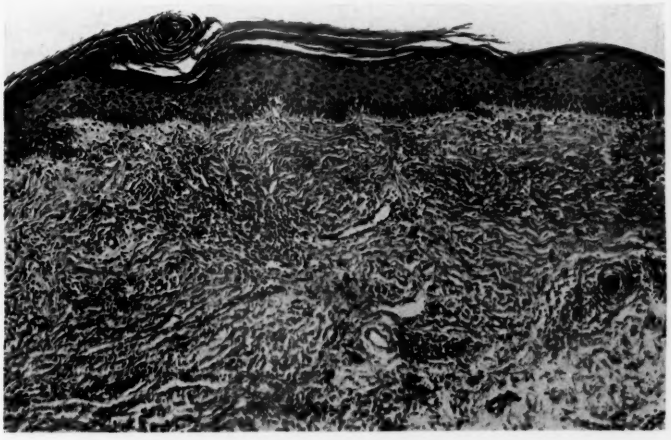


B.

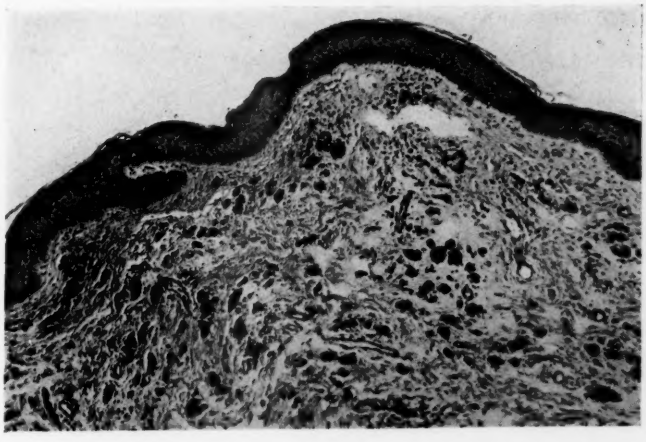
Fig. 2.—Photomicrographs of sections of perineoperianal skin taken one year after tattooing (Case 3). *A*, Section of skin from incompletely tattooed side, showing areas that have either no mercury sulfide or a scant deposit. There was recurrent pruritus on this side. *B*, Sections of skin from the opposite, adequately tattooed nonpruritic side, showing a uniform and abundant subepithelial deposit of mercury sulfide. Foreign body giant cell reaction is not discernible.

variously-sized clumps which have a slight but definite tendency to reach the deeper portion of the cutis (Figs. 1, *B*, *C*, and *D*). Unlike other foreign bodies introduced into the skin, mercury sulfide deposited intracutaneously by tattoo is not accompanied by a foreign body giant cell reaction.

The histologic studies show that the quantity and distribution of the mercury sulfide in the skin can be correlated with its therapeutic effectiveness. For example, a scant subepithelial deposit of mercury sulfide as seen in Fig. 2, *A* is discernible in the skin of the incompletely



A.



B.

Fig. 3.—Photomicrographs of sections of skin removed thirteen and one-half months after tattooing. *A*, Section of skin from perineum (site of recurrence of pruritus), showing scant deposit of mercury sulfide deep in the corium, many leucocytes, and lymphocytes (see text). *B*, Section of skin from well-tattooed nonpruritic (control) area, showing uniform and an abundant subepithelial deposit of mercury sulfide, and moderate infiltration of round cells. Again note the absence of foreign body giant cell reaction.

tattooed anoperineal region which was the site of recurrent, localized areal pruritus. In contrast, the opposite, nonpruritic, adequately-treated anoperineal site of the same patient shows an abundance of mercury sulfide well distributed (Fig. 2, *B*). This is consistent with the clinical observations made previously.[4]

SUMMARY

Histologic studies of skin biopsies of four selected patients tattooed with mercury sulfide for the treatment of intractable localized pruritus are presented. Massive deposition of the mercury sulfide in the upper portion of the corium with some deposit in the epithelium is seen immediately after adequate tattooing. Later on, the mercury sulfide is localized in the corium as clumps of various sizes, which have a slight but definite tendency to reach the deeper portion of the skin. Evidence of foreign body giant cell reaction in the skin commonly seen after the introduction of other foreign substances intracutaneously has not been observed following tattooing with mercury sulfide. It appears that the quantity and the distribution of the mercury sulfide deposited intracutaneously by tattoo can be correlated with its therapeutic effectiveness.

I am indebted to Dr. S. H. Geist for his assistance and encouragement in this work.

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876 PARK AVENUE

SYPHILIS AND UNCONTROLLED FERTILITY

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(From the Milbank Memorial Fund)

RECENT studies have shown that the factors of greatest importance in determining differences in the fertility of large groups of women are those associated with voluntary attempts to control fertility by means of contraception and induced abortion.[5, 8, 9, 11] When the extent of these efforts is known and can be excluded from the experience of a group, it becomes possible to measure the effect of other factors on the uncontrolled fertility of the group.

In the course of a recent study of a group of indigent negro women from a cotton-mill area in the South, it was found that when no attempt had been made to control fertility by means of contraception or induced abortion, the pregnancy rates of women with syphilis, but free from gynecologic or endocrine pathology, were consistently and significantly lower than those of women free from syphilis as well as from the other types of pathology. This finding, so far as I have been able to ascertain, is a new one, and the records of the women under consideration were,

therefore, subjected to detailed analysis, in order to determine, if possible, the reasons for the relatively low uncontrolled fertility of the syphilitic women.

Little is known about the effect of syphilis on uncontrolled fertility.

White and Veeder stated, in 1922, that: "Syphilis in the parents may react upon the succeeding generation in several ways: first, by preventing or inhibiting pregnancy; second, by causing the death of the unborn child; third, by being transmitted to the living child while yet in utero."[14]

Numerous studies have shown that there is a high fetal mortality among the pregnancies of syphilitic women. A few students of the problem have reported a large proportion of childless couples among syphilitic families, but no attempt has been made to determine whether the childlessness was voluntary or was attributable to the syphilis or associated pathology.[7] Physicians treating syphilitic couples would doubtless have advised them to use contraceptive measures both for prophylaxis of the disease and to prevent pregnancy, and it is therefore probable that many of the childless syphilitic couples were childless because of their use of contraceptives.

In studying the records of a group of negro women referred to the Spartanburg (South Carolina) Maternal Health Clinic for contraceptive advice, it was possible to isolate their experience without contraceptives, before they attended the clinic, and to study the association between syphilis and uncontrolled fertility for this group. The result of a blood test for syphilis was entered on the clinic record of every patient. It was found that 25 per cent of the negro women referred to the contraceptive clinic in the years 1935 to 1939 had three- or four-plus Wassermann and/or Kahn reactions, and an additional 6 per cent had one- or two-plus reactions.* The number of records was large enough to permit of separate study of the fertility of the syphilitic women and of factors other than syphilis which might be expected to influence it.

THE DATA

Four hundred fifty-seven negro women were examined and advised at the Spartanburg Maternal Health Clinic during the period of study. About 60 per cent of them were the wives of unskilled or semiskilled workers in Spartanburg or in the cotton mills in the County. The remainder were wives of farm tenants, sharecroppers, or farm laborers. All came from families who were indigent or had very low incomes. Seventy-five per cent of them had made no attempt to practice contraception before they attended the Maternal Health Clinic. They were a highly fertile group, and had averaged 3.5 live births per woman, although their mean length of marriage prior to clinic attendance was only about eight years.

The Maternal Health Clinic is an intramural clinic in the Spartanburg General Hospital, run by the County Health Department. Each woman advised in the contraceptive clinic was referred directly from another hospital service or was examined in the medical clinic before she was

*In a study of a negro population of a rural county in Tennessee, Crabtree and Bishop[2] found that 32.6 per cent of the negroes, 15-65 years of age, had positive Wassermann reactions.

accepted in the Maternal Health Clinic. Each record, therefore, included a digest of the medical history and diagnosis, as well as reports of laboratory tests. At the Maternal Health Clinic each woman was given a complete pelvic examination.

The record of each patient contained a fertility history which included the date and type of termination of each pregnancy and information concerning the use of contraception, if any, which preceded it. The women were also questioned about the length of lactation following each live birth and of post-partum amenorrhea following each delivery.

The patients were classified into three groups: (1) women whose records showed no evidence of inflammatory conditions in the pelvis, of endocrine disease, of pellagra, or of syphilis; this will be designated hereinafter as the "nonpathologic" group; (2) women with any evidence of pelvic inflammation, of endocrine pathology, or of pellagra, including those who had syphilis in addition to the other types of pathology; and (3) women who had positive Wassermann reactions and/or a diagnosis of syphilis or a history of syphilis but had no other disease which might be presumed to affect their fertility. For the purposes of the present study we are concerned only with the first and third groups.

In order to eliminate the possible influence of pelvic pathology, following gonorrheal or other pelvic infection, on the fertility of the women under consideration, all women with definite evidence of pelvic inflammation or with positive smears for gonorrhea were excluded from the two samples selected for study. The pelvic findings for women with no evidence of disease and for women with syphilis only are compared in Table I.

TABLE I. PROPORTIONS OF NEGRO WOMEN WITH AND WITHOUT SYPHILIS WHO HAD CERTAIN TYPES OF PELVIC PATHOLOGY

TYPE OF PATHOLOGY	WOMEN WITHOUT PATHOLOGY WHICH MIGHT BE EXPECTED TO AFFECT FERTILITY	WOMEN WITH SYPHILIS BUT FREE FROM SERIOUS PELVIC OR ENDOCRINE PATHOLOGY
	NUMBER OF WOMEN EXAMINED*	
	241	111
	PER CENT WITH EACH TYPE OF PATHOLOGY	
Cervix lacerated (no inflammation)	78.6	75.7
Cervix lacerated and inflamed	14.3	13.5
Cervix inflamed (no laceration)	1.3	1.8
Uterus retroflexed and/or retroverted	63.9	58.9
Uterine masses and/or tenderness	0.4	1.9
One or both tubes tender and/or painful	2.1	4.5
One or both ovaries tender and/or painful	2.5	3.6
Smear positive for gonorrhea	0.0	0.0
Smear doubtful for gonorrhea	1.3	1.9

*The number of women in each group who had complete pelvic examinations was less than the number shown. In each instance the proportion shown is based on the number for whom the specific organ was examined.

The prevalence of cervical inflammation and pain and/or tenderness of the uterus and adnexa was low in both groups. It was slightly but not significantly higher for the syphilitic women than for the nonpathological group. Malposition of the uterus, on the other hand, was slightly more prevalent among the women free from pathology. The data in

Table I show quite clearly that differences in the prevalence of pelvic pathology were not great enough to account for differences in the fertility of the two groups.

Pregnancy and birth rates were computed separately for exposures without contraception for each of the groups under consideration.* On the basis of these pregnancy and birth rates, it was estimated that a theoretical woman whose uncontrolled fertility represented the average of that exhibited by the nonpathologic group, who was married at fifteen and who used no contraception until she entered the menopause at forty-five, would have had 15 pregnancies, terminating in 13 live births during the thirty fertile years of her married life.† The "average" woman with syphilis would have had only 13 pregnancies and 10 live births in a similar thirty-year period. These figures show quite graphically that syphilis was associated with a reduction in uncontrolled fertility in this group; that women with syphilis not only conceived less rapidly than women free from pathology, but that their birth rate was much lower because of the higher rate of fetal mortality in syphilis. The difference in the number of live births expected in the syphilitic as compared with the nonpathologic families is small in terms of expected size of family, but actually represents a reduction of 23 per cent in effective fertility.

It has been shown that the relatively low birth rate of the syphilitic women was to some extent attributable to the high fetal mortality in syphilitic pregnancies. The distributions of pregnancy terminations for the Spartanburg negroes, with and without syphilis, are compared with those for similarly selected groups of negro women in two other areas in Table II.‡ The proportion of pregnancies terminating in stillbirths and abortions was very much higher in the syphilitic than in the nonsyphilitic groups (Fig. 1).

About 50 per cent of the syphilitic women who attended the Spartanburg Clinic had each had at least one abortion or stillbirth. On the other hand, only 29 per cent of the women free from pathology had had any abortions or stillbirths. Solomon and Solomon reported that, among syphilitic families in which the wife had a positive Wassermann reaction, 52.2 per cent of the women who had had any pregnancies had had one or more stillbirths or abortions. In the families in which only the husband's Wassermann reaction was positive, only 20 per cent had had any abortions or stillbirths.§

Pregnancy wastage, though important, is only one factor in the decreased fertility of women with syphilis. It has been shown that the

*It must be borne in mind that the information on the fertility of the women studied was in the form of a history covering a period antedating the initial contact with the Maternal Health Clinic by lengths of time varying from one month to more than twenty years. The information concerning the Wassermann or Kahn reaction related only to the date of examination, which coincided with the initial clinic contact. To the extent that some women in the "nonpathologic" group may have had syphilis and recovered from it, and that some women in the "syphilis" group may have acquired syphilis late in their married life, the records probably do not represent the total experience of groups continuously free of pathology or continuously infected with syphilis. The presumptive presence of a few cases of healed syphilis in the "nonpathologic" group and of periods free of syphilis in the experience of the "syphilitic" group would to some extent minimize any differences in fertility attributable to the presence of syphilis.

†For the method of computing these theoretical rates, *see* Stix and Notestein,[11] pp. 32, 33, and Table 10.

‡The pregnancy wastage reported for the nonsyphilitic women in New York and Tennessee appears to be low, and there may have been some under-reporting of abortions and stillbirths in these groups. For comparable figures from studies of white women, *see* Stix and Notestein,[11] Tables 30 and 31; Stix and Wiehl,[12] Table I; and Wiehl,[16] Table II.

§Solomon and Solomon,[7] 1922, Table 30. The latter figure was derived from data presented in the table.

TABLE II. DISTRIBUTION OF PREGNANCY TERMINATIONS FOR NEGRO WOMEN WITH AND WITHOUT SYPHILIS IN THREE AREAS

SOURCE OF MATERIAL AND YEAR OF SURVEY	PERCENTAGE OF PREGNANCY TERMINATIONS OF EACH TYPE							NUMBER OF PREGNANCIES
	TOTAL	LIVE BIRTHS	NONVOLUNTARY PREGNANCY WASTAGE				ILLEGAL ABORTIONS	
			TOTAL	STILLBIRTHS	SPONTANEOUS ABORTIONS	THERAPEUTIC ABORTIONS		
	Women With Syphilis							
Spartanburg County, South Carolina, 1935-1939*	100.0	73.4	25.7	11.2	14.5	0.0	0.9	447
New York, New York, 1923**	99.9	79.1	20.9‡					737
Tipton County, Tennessee, 1930†	100.0	72.9	27.1	8.9	18.2§			859
	Women Free From Syphilis							
Spartanburg County, South Carolina, 1935-1939*	100.0	86.9	13.1	3.9	8.9	0.2	0.1	1,446
New York, New York, 1923**	100.0	94.9	5.1‡					948
Tipton County, Tennessee, 1930†	100.0	96.7	3.3	0.4	2.9§			243

*The figures relate to all pregnancies, including those occurring when contraception was used. The distribution of terminations of pregnancies occurring during exposures without contraception did not differ significantly from the distribution of total pregnancies.

**Health Work for Mothers and Children in a Colored Community. New York Association for Improving the Condition of the Poor. Publication 131, 1924, Tables VIII and IX.

†Crabtree, James A., and Bishop, E. L.: Syphilis in a Rural Negro Population in Tennessee, Am. J. Public Health 22: 157-162, 1932, Table V.

‡Includes all abortions and stillbirths.

§All abortions.

"average" woman with syphilis in the Spartanburg group would have had only 13 pregnancies in the same period during which the woman without pathology would have had 15. Fig. 2 and Table III show the pregnancy rates per 100 years of exposure to the risk of pregnancy for the entire preclinic experience without contraceptives of these two groups of women.*

The rates shown in Fig. 2 and Table III are derived from the total preclinic experience of the syphilitic and of the nonpathologic groups. Because of the possibility of bias inherent in this use of the data (see footnote p. 299) rates were computed separately for experience falling within a five-year period preceding the initial clinic contact. The rates for the period were 80 pregnancies per 100 years of exposure to risk

*The concept of exposure to the risk of pregnancy is based on the assumption that women are exposed to the risk of becoming pregnant for that part of the period between menarche and menopause during which they are habitually having coitus, as in the marital state, and are not pregnant or in the puerperium. The length of exposure for each woman is computed by deducting from the total number of months between marriage and the date of record ten months for each full-term birth and a month in addition to the reported period of gestation for each abortion or premature birth, as well as all periods of abstinence or separation of husband and wife. Pregnancy rates are then derived by summing the pregnancies and the total number of years of exposure of the group and dividing the number of pregnancies by the number of years of exposure to risk. The quotient is then multiplied by 100 in order to have a rate expressed in whole numbers. For further details, *see* Stix and Notestein,[11] Appendix III.

for syphilitic women and 131 pregnancies per 100 years of exposure for women without pathology. These rates showed a greater difference than those for the total preclinic experience, for which the corresponding rates were 80 and 108.*

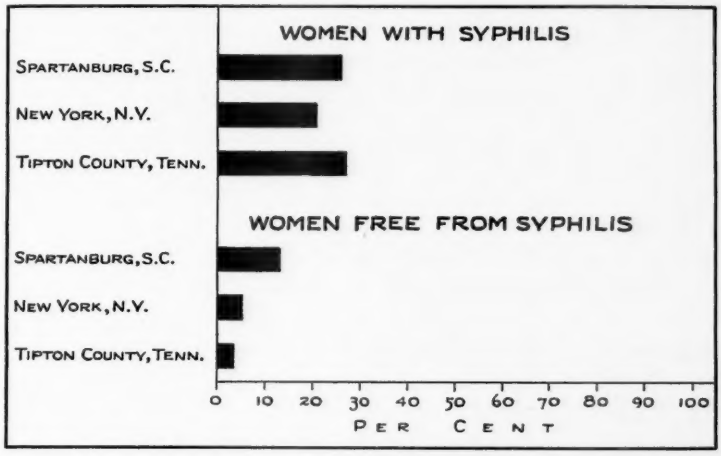

Fig. 1.—Percentage of pregnancies terminating in stillbirths and abortions for negro women with and without syphilis in three areas.

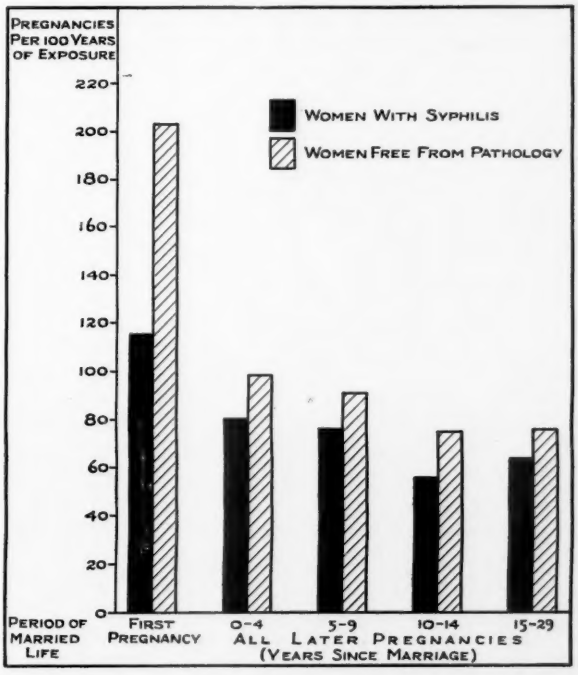

Fig. 2.—Pregnancy rates for negro women with and without syphilis, when no contraception was used.

*Both sets of rates were standardized to the period-of-married-life distribution of the combined exposures of the two groups of women for the five-year period immediately preceding attendance at the clinic.

TABLE III. PREGNANCY RATES FOR NEGRO WOMEN WITH AND WITHOUT SYPHILIS WHEN NO ATTEMPT WAS MADE TO USE CONTRACEPTION

PERIOD OF MARRIED LIFE*	WOMEN WITH SYPHILIS, BUT FREE FROM OTHER TYPES OF PATHOLOGY		WOMEN FREE FROM SYPHILIS AND PELVIC OR ENDOCRINE PATHOLOGY	
	PREGNANCIES PER 100 YEARS OF EXPOSURE TO THE RISK OF PREGNANCY			
First pregnancy	116		203	
All later pregnancies: Total	74		91	
(Years since marriage)				
0- 4	81		99	
5- 9	77		91	
10-14	56		75	
15-29	64		76	
	NUMBER OF YEARS OF EXPOSURE AND NUMBER OF PREGNANCIES			
	EXPOSURE IN YEARS	NUMBER OF PREGNANCIES	EXPOSURE IN YEARS	NUMBER OF PREGNANCIES
First pregnancy	73.1	85	93.4	190
All later pregnancies: Total	373.2	277	775.8	709
(Years since marriage)				
0- 4	161.1	130	360.4	358
5- 9	126.3	97	245.8	223
10-14	62.2	35	113.2	85
15-29	23.5	15	56.4	43

*A few women in the group were unmarried, and a number of others had premarital pregnancies. Whenever the information was available, exposure was computed from the date of first coitus. Where information concerning premarital experience was not available, the pregnancies for which exposure was unknown were excluded from the tabulations.

Both types of tabulation demonstrate clearly that the rates of the women with syphilis were consistently and significantly lower than the rates of the women without pathology. In other words, the women with syphilis conceived less rapidly than the women without pathology when both groups made no attempt to control conception. In the case of first pregnancies, 64 per cent of the women without demonstrable pathology conceived within three months of marriage, while only about 50 per cent of the women with syphilis conceived within that period. The low rates of the syphilitic women, after the first pregnancy, were not associated with longer periods of post-partum amenorrhea than those reported by the nonpathologic group. In fact, only about 25 per cent of the noncontraceptive exposure of the syphilitic group, as compared with 38 per cent of the exposure of the nonpathologic group, coincided with periods of amenorrhea. The large proportion of stillbirths and abortions among the pregnancies of syphilitic women probably accounted for this situation. These figures show that increased post-partum amenorrhea was not a factor in the low fertility of the syphilitic women.

COMMENT

It is difficult to determine just what factors were involved in the reduced fertility of the couples with syphilis. It is possible that at least part of the reduction may have been due to early, undetected and unreported abortion. It is also possible that the husbands of the syphilitic women may have been responsible to some extent for their low fertility.

It is known that few, if any, of the husbands were absolutely sterile, since only five of the syphilitic women had had no pregnancies. Three of these women had been married for less than a year, and the others for less than four years. It is possible, however, that in the group in which the wives had syphilis, the husbands may have had temporary periods of sterility due to gonorrheal infection, even though the wives showed no evidence of gonorrheal infection or its sequelae when they were examined at the clinic.

The reduction in fertility observed in the syphilitic group is small but significant. Further research is necessary to determine whether other groups with syphilis also exhibit relatively low uncontrolled fertility rates.

CONCLUSION

It has been shown that a group of negro women with positive Wassermann reactions not only had a higher rate of fetal loss than women who were free from syphilis, but also conceived less rapidly than women free from pathology, when no attempt was made to control their fertility. It must be borne in mind, however, that the "relatively low" uncontrolled fertility demonstrated for the syphilitic women under consideration was actually high in terms of potential family size. It is clear, therefore, that any reduction in uncontrolled fertility associated with the presence of syphilis, while it may serve to throw some light on the relatively low birth rates of some negro groups, is insufficient to warrant a change in the routine prescription of contraception for patients with active syphilis.

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ADENOCARCINOMA OF THE VULVA

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CARCINOMA of the vulva is not a rare disease. The majority of carcinomas in this region are naturally of the squamous cell type. Adenocarcinomas are much rarer. The glandular structures which normally are present in the vulva are sweat glands and mucus glands which form the gland of Bartholin. Sweat glands are numerous in the vulva and are of two types, the ordinary or eccrine and the exocrine or apocrine type. Occasionally, other glandular elements are found in the vulva in the nature of accessory breast tissue and remnants of the Wolffian ducts.

Several types of glandular neoplasms in the vulva have been described. The commonest type of glandular neoplasm is that which is described in the German literature as "hidradenoma vulvae." Pick applied this term in 1904 to certain adenomas of the vulva. He was able to trace the connection between these tumors and sweat glands, but expressed the opinion that they originate from rudimentary rather than normal sweat glands. Similar cases have been reported by Hoeck, by Blau, and by Woringer. Burg, in 1930, was able to find reports of 15 cases of hidradenoma in the literature, to which he added one. All except 2 cases were considered as benign. Eichenberg, in 1934, described 12 papillary adenomas of the vulva, all of which belonged in the group of hidradenomas. In addition to these cases which he believed were benign, he described one case which he interpreted as showing malignant changes. He considered that all these neoplasms had originated from sweat glands. Folsome, in 1940, expressed the opinion that 27 per cent of these neoplasms were malignant.

Other types of glandular neoplasms in the vulva have been described. A case of adenocarcinoma of the vulva was described by Greene in 1936, associated with a squamous cell carcinoma of the vulva in which the adenocarcinoma was thought to have arisen from aberrant breast tissue. Fossel, in 1935, described a case of cylindroma of the vulva.

MATERIAL

Thirty-two tumors which had been removed from 31 patients are included in this study. These constituted all the primary adenocarcinomas of the vulva which had been removed at the Mayo Clinic from 1906 to 1939, inclusive. Since the majority of these tumors were small, microscopic sections could be made which included a cross section of the entire tumor. Histologic sections stained with hematoxylin and eosin were studied. Occasionally, special stains were utilized. The clinical records on these patients were reviewed, for the most part, independent of the histopathologic studies.

Thirty of the neoplasms were papillary adenocarcinomas, and because of this have been grouped together. One was a fairly malignant solid adenocarcinoma which did not appear to belong in the first group. Another was an adenocarcinoma which appeared to be of the cylindroma type.

CLINICAL DATA

Papillary Adenocarcinoma.—The 30 neoplasms in this group were removed from 29 patients. Several of these neoplasms were unsuspected by the patient and were recognized only on physical examination. In the cases in which the tumor had been noticed by the patient, the tumor had been present in the majority of instances for many years. The usual clinical course was that the tumor had increased in size very slowly. Some tumors were not recognized by the patient or on physical examination, but were found and excised during the course of some perineal surgical procedure.

In several instances, the subjective symptom of pain was present because the surface epithelium over the tumor had ulcerated. The majority of these neoplasms were diagnosed clinically as sebaceous cysts, largely owing to the fact that many of these presented a cystic appearance.

In every instance except one, the tumor was confined to the labium majus. In one case, however, the lesion was fairly extensive, involving not only one labium but a portion of the vaginal wall and the perineal body. All of the remaining neoplasms measured 1 cm. in diameter or less.

None of the patients in this group were less than 32 years of age. The oldest patient was 67 years of age.

Excision of the tumor was sufficient in every instance to effect a cure. In most cases, a portion of the surrounding nonneoplastic tissue was removed with the tumor. In the one case in this group in which the tumor was extensive, excision by cautery of the affected vulva, vaginal wall, and perineal body resulted in a cure. The patient died sixteen years later from an unrelated condition, and up to the time of death there was no evidence of recurrence. Radium or roentgen therapy was not used in any case.

Miscellaneous Adenocarcinomas.—Two unrelated adenocarcinomas comprise this group. The only point of similarity is that neither one is papillary. The first tumor is an ordinary adenocarcinoma of a fairly malignant type and the second is an adenocarcinoma of the cylindroma type. The first adenocarcinoma was removed from a 22-year-old woman who had first noticed the tumor nine months previously. It had been excised elsewhere and roentgen therapy had been applied. On examination, the mass in the labium majus measured 4 cm. in diameter with involvement of the inguinal lymph nodes. Partial vulvectomy was performed together with bilateral dissection of the inguinal nodes. Postoperative roentgen therapy was completed. The patient died four months later.

The second adenocarcinoma, which was of the cylindroma type, was removed from a 36-year-old woman who had noticed a tumor in the posterior portion of the labium majus four years previously. There had been a gradual increase in size. Wide excision of the tumor was done, followed by radium and roentgen therapy. Seven years after this, a recurrent tumor was excised. Seven years after the second operation, the neoplasm apparently was arrested, although there was a small nodule in the old scar, the nature of which had not been determined.

GROSS APPEARANCE

Approximately 60 per cent of the papillary adenocarcinomas were found within cysts. The remaining 40 per cent were solid. The two carcinomas belonging in the miscellaneous group were also solid.

HISTOLOGIC APPEARANCE

Papillary Adenocarcinomas.—Well-formed acini were present in all the neoplasms in this group. In addition to the acini, papillary projections could be demonstrated readily in all these tumors. The nuclei were fairly large, slightly irregular, and hyperchromatic. Mitotic figures could be demonstrated but were scarce. All of these features are indicative of a slowly growing neoplasm. It is not surprising, then, that all of these carcinomas were Graded 1 or 2, using Broders' criteria. Twenty-eight of the 30 neoplasms in this group were Graded 1 and 2 were Graded 2.

In those specimens in which the tumor was found within a cyst, the neoplasm was attached at one or more points to the wall, often by a narrow stalk. The capsule of the cyst occasionally was invaded by the tumor cells.

In 12 of the 30 neoplasms, it was possible to demonstrate, within the tumor, acini in which the papillary projections were very prominent and in which the cytoplasm of the cells was strikingly eosinophilic and granular (Figs. 1 and 2). In all 12 cases, this peculiar epithelium could be traced into cells whose cytoplasm was not eosinophilic and which were definitely carcinomatous. The appearance of these peculiar glands corresponds in practically every detail to that of apocrine sweat glands (Figs. 3 and 4).

In 2 additional cases, apocrine glands were demonstrable adjacent to the papillary adenocarcinoma but were not incorporated in the neoplasm. The remaining papillary carcinomas, except for the presence of apocrine sweat glands, corresponded in histologic detail to the others.

In no instance could any connection be demonstrated between the mucus glands which form the gland of Bartholin and the adenocarcinomas in this group. In every instance, the carcinoma was situated on the labium majus, and in the majority the carcinoma was situated anterior to the usual site of the gland of Bartholin.

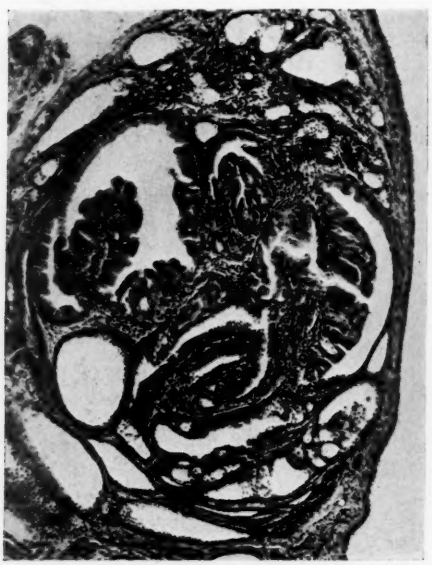

Fig. 1.

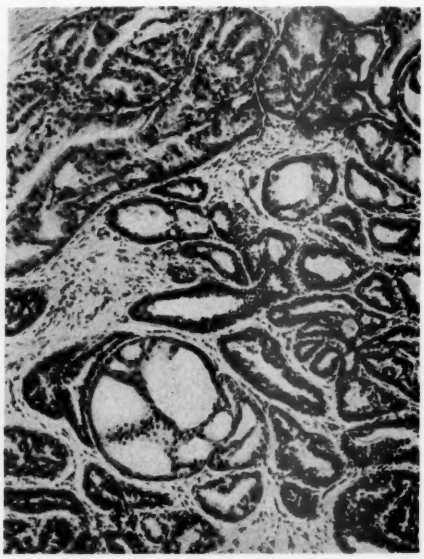

Fig. 2.

Fig. 1.—Papillary adenocarcinoma. The transition between the clear cells of the apocrine sweat glands and the carcinoma cells can be seen (hematoxylin and eosin ×65).

Fig. 2.—Papillary adenocarcinoma of the vulva. The epithelium of a portion of the tumor shows pale cytoplasm characteristic of apocrine sweat glands (hematoxylin and eosin ×80).

All papillary carcinomas which were small enough to localize in this group were situated in the corium immediately subjacent to the epidermis. As would be expected with a tumor in the corium, interference with the blood supply to the epidermis overlying the tumor occurred in several of these neoplasms with resulting ulceration of the epithelium.

Miscellaneous Group.—The two neoplasms in this group presented different histopathologic pictures. The first tumor was an adenocarcinoma with large irregular and very hyperchromatic nuclei in which mitotic figures were very abundant (Fig. 5). The metastatic growths in the lymph nodes presented an identical picture. This adenocarcinoma was Graded 3. The second tumor was an adenocarcinoma of the cylindroma type (Fig. 6). The cells were arranged in columns form-

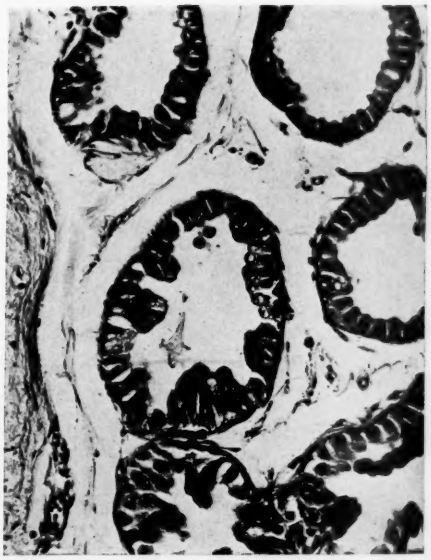

Fig. 3.

Fig. 4.

Fig. 3.—Apocrine sweat glands showing the two layers of cell and the characteristic papillary infoldings (hematoxylin and eosin ×185).

Fig. 4.—Apocrine sweat gland showing the close association with a hair follicle (hematoxylin and eosin ×95).

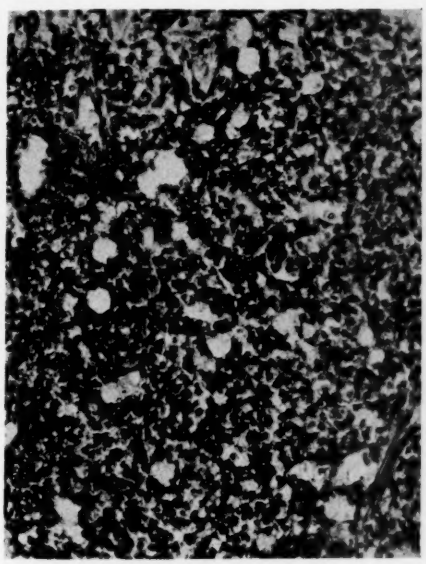

Fig. 5.

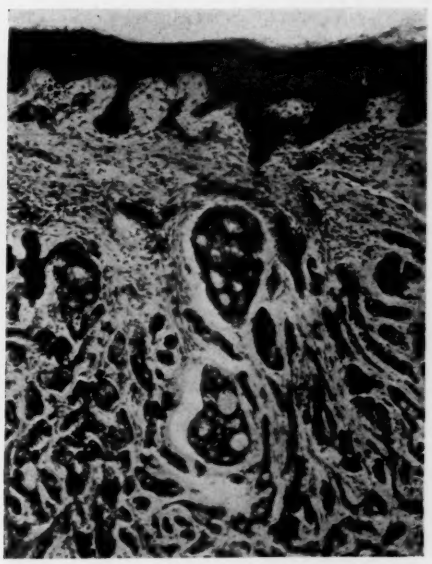

Fig. 6.

Fig. 5.—Adenocarcinoma of vulva. The neoplasm is not papillary (hematoxylin and eosin ×155).

Fig. 6.—Grade 1 adenocarcinoma of the cylindroma type (hematoxylin and eosin ×85).

ing poorly shaped acini. The individual cells were fairly small and had fairly regular nuclei. Mitotic figures were not numerous. This adenocarcinoma was Graded 1.

COMMENT

One can reasonably assume that practically all, if not all, papillary adenocarcinomas in the vulva are derived from apocrine sweat glands. This statement seems justified, since it has been shown that one-third of the papillary adenocarcinomas contained apocrine sweat glands. Additional support is offered by the fact that those papillary carcinomas which were small enough to localize were located in the corium of the vulva, which is the location of normal apocrine glands.

Several German authors have derived these neoplasms in the vulva from sweat glands. However, these authors did not derive these specifically from apocrine sweat glands, but rather from rudimentary sweat glands.

Apocrine sweat glands have been known for almost a century (Horner). These sweat glands, according to Homma, arise from the hair follicles. They are more numerous in negroes than in the white race. They are found in the axilla, in the perianal region, and around the perineum. Less commonly, they are found in other locations of the body such as the areola of the breast and the scalp. They are distributed widely in lower animals, according to Woollard. Whereas, the eccrine or exocrine glands secrete sweat without admixture of cell contents, the secretion from apocrine glands is formed by extrusion of a portion of the cytoplasm of the cell. Particularly in lower animals, the apocrine glands have a very definite function to perform in connection with sex instinct.

The similarity between these papillary adenocarcinomas of the vulva and intraductal papillary adenocarcinomas of the breast is evident. This is not surprising, since the breast is supposed to develop from apocrine sweat glands, according to some authorities.

The solid carcinoma of a higher grade of malignancy which metastasized seemed to represent a separate type of neoplasm; however, it is possible that this is of similar origin to the papillary carcinomas and that it is merely more malignant. This fact could not be proved.

The problem can be brought up as to whether these papillary neoplasms represent true carcinomas or not. Because of their histologic character, it would seem better to refer to them as adenocarcinomas of a low grade of malignancy rather than simple adenomas. Metastatic growths were not found in any of the cases of papillary carcinoma. However, it would appear probable that if a sufficient number of these cases were studied, metastatic growths would be found eventually.

From a practical standpoint it can be stated that because of the slow growth of the tumor and the slow tendency to metastasize, complete excision of the tumor together with a portion of the surrounding tissue is sufficient to effect a cure in these papillary carcinomas.

Adenocarcinomas of the cylindroma type are slow-growing neoplasms which are frequently difficult to eradicate because of local extension. The origin in this particular case of cylindroma could not be determined from the histopathologic studies. Montgomery and Kierland have been

able to trace the connection between several of these tumors and the basal cells of the epidermis. They expressed the belief that they do not take their origin from sweat glands. Other authors derive these neoplasms from sweat glands, hair follicles, and sebaceous glands.

SUMMARY

Thirty-two adenocarcinomas of the vulva have been described. Of these, 30 were papillary carcinomas which originated from the apocrine sweat glands in this location. One was a nonpapillary adenocarcinoma and one an adenocarcinoma of the cylindroma type. The papillary carcinomas did not show a tendency to metastasize and were cured by simple excision of the neoplasm.

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BENIGN TUMORS OF VULVA*

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THE vulva includes the labia majora, labia minora, mons pubis, clitoris, and those structures contained in the labia, including the glands of Bartholin. Because of the variety of tissues in this region, benign neoplasms of the vulva are an interesting group.

Leonard, in 1917, pointed out that fibroma was the most common tumor of the vulva. He found 6 cases of fibroma of the vulva among 23,000 gynecologic cases at Johns Hopkins Hospital and reviewed 103 cases which had been reported in the literature to that time. The majority of these tumors were found during the childbearing age of the patient. Frequently, the tumor was found to enlarge during the period of menstrual flow. Leonard expressed the opinion that these tumors originated either from the connective tissue of the vulva or from the round ligament. Sarcomatous change was reported in 19 of the 103 cases. In 1929, Brady collected 175 cases of fibroma of the vulva from the literature.

In 1893, Kelly reviewed from the literature 20 cases of lipoma of the vulva. He pointed out that the lipomas were likely to simulate inguinal hernia. Endometriomas of the labia majora have been found in close connection with the round ligament. Such a case was reported by Jeffcoate in 1937. Accessory breast tissue has been reported in the vulva by several investigators, including Bell, McFarland

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and Mengert. Such tissue frequently was discovered during pregnancy because of its painful enlargement as a result of lactation. A fibroadenoma was reported in breast tissue in the vulva by Friedel in 1932.

Thirty-four neoplasms of the vulva were studied as the basis of this report. These represented tumors which had been removed from the vulva at the Mayo Clinic from 1906 to 1939 inclusive, specimens of which were available for study. The records of this series of cases were reviewed and pertinent details noted. Microscopic sections were studied; hematoxylin and eosin or any special stains which seemed indicated were employed. Endometriosis, accessory breast tissue, condylomas, epidermoid cysts and moles were not included because none except the last are true neoplasms. Moles were not included because of their common occurrence.

The 34 neoplasms presented 7 histologic types which included 16 fibromas, 7 lipomas, 5 hemangiomas, 2 neurofibromas, two leiomyomas, one ganglioneuroma, and one lymphangioma.

CLINICAL FEATURES

Lack of clinical symptoms in cases of benign tumors of the vulva was an outstanding feature. Many of the smaller tumors were not noticed by the patient but were discovered on routine physical examination. Some of the larger tumors caused mechanical difficulties. Pain occasionally was present, and in such cases ulceration of the epithelium overlying the tumor usually could be demonstrated. This ulceration can be explained readily on the basis of a decreased blood supply to the epithelium overlying the neoplasm. Many patients who noticed these tumors were worried concerning the possibility of malignant change in the tumor, because it had become larger over a period of years. In many cases, this was the sole factor which caused the patient to seek the services of a physician.

A study of the ages of the patients in this series did not reveal anything significant. The youngest patient was sixteen years of age and the oldest sixty-nine. Although the majority of patients were of childbearing age, 10 were more than fifty years of age.

PATHOLOGY

The 16 fibromas varied from 6 mm. to 8 cm. in diameter. The surface of several of the larger ones was ulcerated. Several different histologic pictures were found. The majority of tumors were made up of fairly adult fibroblasts which formed spindle cells. Mitotic figures were not demonstrated in any of the fibromas and myxomatous degeneration was a common finding (Fig. 1). Although several of the fibromas were cellular, none were considered sarcomatous. One patient related that the tumor had increased in size during two terms of pregnancy. Although a careful search of the specimen was made for breast tissue, none was found.

Seven lipomas were studied in this group. All represented single tumors in the vulva, but in one case, in addition to the single lipoma in the vulva, multiple lipomas were situated in the anterior abdominal wall. The most bulky tumors of any in this series were lipomas. One measured 17 cm. in diameter.

Because of the marked vascularity of the tissues of the vulva, it is not surprising that five of the tumors were hemangiomas. Because of the cavernous spaces normally found in the vulva, it was necessary to confine the diagnosis of hemangioma to a definite tumor composed of large, irregular, blood vascular spaces between which smooth muscle was not found (Fig. 2). The largest hemangioma measured 5 cm. in diameter. One was situated on the clitoris, the remainder on the labia majora. The surface epithelium of one hemangioma was ulcerated. The majority were of the cavernous type, exhibiting large blood spaces lined with a single layer of endothelium.

The two leiomyomas encountered appeared grossly like leiomyomas of the uterus. The tumors were definitely encapsulated and one was lobulated. The whorling appearance of the cells, characteristic of leiomyoma, was evident. One tumor measured 6 by 3.5 by 3.5 cm., and the other measured approximately 4 cm. in diameter. Microscopically, both were composed of bundles of smooth muscle, with some fibrosis between the bundles (Fig. 3).

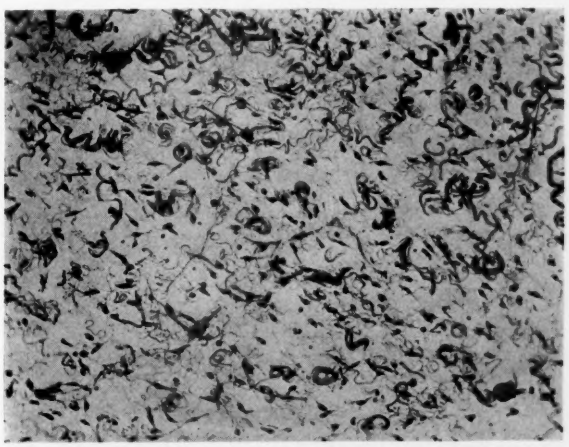

Fig. 1.—Fibroma of the vulva in which marked myxomatous degeneration can be seen (hematoxylin and eosin ×80).

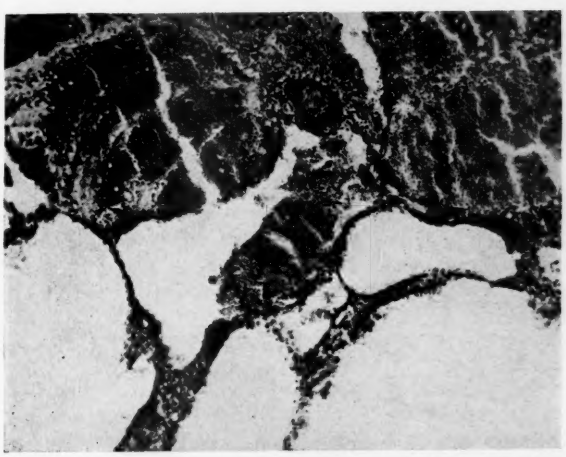

Fig. 2.—Hemangioma of vulva in which large cavernous spaces can be seen (hematoxylin and eosin ×80).

The two neurofibromas were small; one measured 2 cm. in diameter and the other 1.5 cm. Pain was not a clinical feature in either case. On microscopic study, palisading of the nuclei could be seen. One neurofibroma was associated with a small cyst lined with squamous epithelium.

The ganglioneuroma included in this series measured 1.5 by 0.9 by 0.6 cm. Subjective symptoms were not produced by this lesion. The cells had prominent nucleoli and were arranged in the form of rosettes (Fig. 4). Nissl's bodies could be demonstrated in the cells when cresyl violet stain was employed.

One lymphangioma was demonstrated, which measured 7 mm. in diameter. Histologically, it consisted of a meshwork of lymphatic vessels.

COMMENT

It is not surprising that benign tumors situated in the vulva produce so few symptoms. The vulva is a region of the body not seen by the patient; and swelling in this region does not in itself produce symptoms of pressure. Subjective symptoms were lacking except when ulceration of the epithelium occurred, in which case pain was caused by infection.

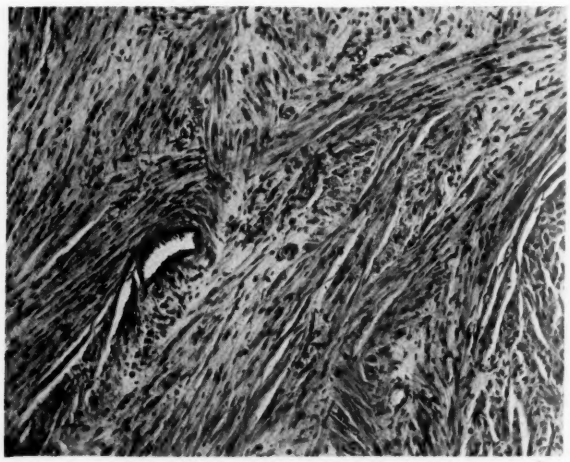

Fig. 3.—Leiomyoma of the vulva in which bundles of nonstriated muscle are evident (hematoxylin and eosin ×80).

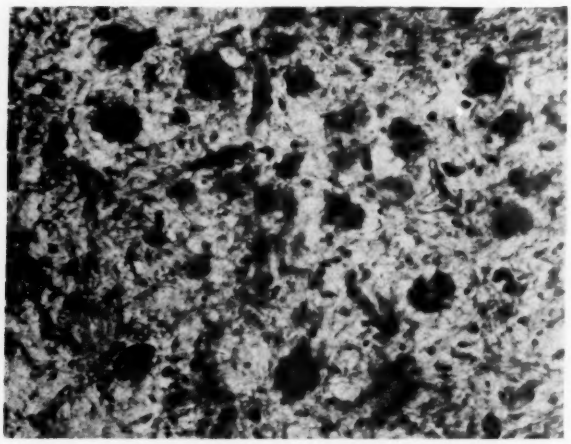

Fig. 4.—Ganglioneuroma of the vulva in which the ganglion cells are arranged in rosettes (hematoxylin and eosin ×210).

Evidence of sarcomatous change was not found in any of these neoplasms. This fact was apparent on histologic examination, and is further substantiated by the fact that in none of the cases in this series did the tumor recur.

The origin of the two leiomyomas in this group present an interesting problem. Smooth muscle is present in the vulva in the round ligament and erectile tissue. Each of these tumors was situated on the labium majus, too far posteriorly to have originated from the round ligament.

It is not surprising that hemangiomas and neurofibromas are found in the vulva because of the generous supply of blood vessels and nerves. The ganglioneuroma in this group is interesting only from a histopathologic standpoint, as it produced no subjective symptoms.

There is another group of tumors of the vulva which have been referred to in the literature as hidradenomas or tumors of the sweat gland. These neoplasms probably should be referred to as papillary adenocarcinomas rather than benign adenomas because of their histologic appearance and malignant potentialities. For these reasons, these tumors were not included in this series of benign neoplasms.

SUMMARY

Thirty-four benign neoplasms of the vulva encountered at the Mayo Clinic were studied. It was found that the commonest types of tumors were fibromas, lipomas, and hemangiomas, in the order named. Two neurofibromas, two leiomyomas, a ganglioneuroma and a lymphangioma also were encountered.

An outstanding feature was the lack of symptoms produced by the tumor in the majority of cases.

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Brown, Preston T., and Pennington, John W.: Pelvic Symptoms of Urinary Tract Origin, J. A. M. A. **116**: 189, 1941.

The authors stress the importance of ruling out urinary tract pathology in the diagnosis of the pelvic symptom complex. Genital diseases may be simulated by ureteral or urethral stricture, contracture of the vesical orifice, chronic urethritis and trigonitis, and rarely by ptosis of the kidney. Dysmenorrhea may be caused by ureteral stricture. A sensation of prolapse and pressure in the pelvis with actual descensus is strongly suggestive of some bladder or ureteral disorder. Urography, especially the intravenous method, is of vital importance in the diagnosis. Complete endoscopic examination and the determination of bladder capacity is also important. The authors conclude that it is the duty of the surgeon to make a careful and complete study of the urinary tract before ascribing obscure pelvic symptoms to uncomplicated retroversion, cystic ovaries, chronic cervicitis, or even more clear-cut forms of pelvic disease.

William Berman.

MYOMA OF THE VAGINA

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MYOMA* arising from the vaginal wall is a rare condition and, since the first case was reported by Denys de Leyden[1] in 1733, not more than 200 authentic cases have been described in the literature. The condition is of interest because of its rarity and of importance because of the unusual problems which may arise in connection with its diagnosis. Because of the variety of sizes, appearances and locations of vaginal myomas, the condition has been variously mistaken for sarcoma,[2] carcinoma,[3] vaginal cyst (authors' Case 12), prolapsus uteri,[4, 19] cystocele,[5, 6] and adenomyoma of the vagina.[7] Notwithstanding the importance of this group of tumors in gynecologic diagnosis, little attention has been given the subject in textbooks of gynecology, and the only comprehensive reports appearing in the American or English literature were published by Phillips[23] in 1899, and by R. R. Smith[8] in 1902.

The subject was first reviewed by Kleinwächter[9] who, in 1882, reported 53 cases. Additional case reports and reviews were made by Phillips and Smith, and still others by Müller[10] and Stein.[11] Nürnberger[12] critically reviewed the literature in 1930 and considered only 130 cases of myoma of the vagina to be well authenticated. In contrast with this conservative estimate, Tourneux,[1] in 1934, accepted 160 cases reported by Potel[13] in 1903, and estimated that about 140 other satisfactory cases have since been recorded. Since Tourneux' review only occasional case reports have been published.

We have reviewed the material in the files of our laboratory for the past fifty years and have found 9 cases of primary myoma of the vagina, one of which (Case 1) has been reported previously by Kelly and Cullen.[14] We have been fortunate enough to obtain material and notes on three additional cases from the private files of T. S. Cullen, R. W. TeLinde, and Emil Novak. The important features of these twelve cases are presented below in tabular form (Table I) and discussed.

INCIDENCE

The rarity of vaginal myomas is apparent when it is realized that only nine cases can be found in a gynecologic laboratory which contains more than 50,000 case specimens, including 19 cases of primary carcinoma of the vagina, 8 cases of primary sarcoma of the vagina and more than 100 vaginal cysts. A review of more than 15,000 autopsies performed in the Johns Hopkins Hospital reveals only one case of vaginal myoma. Similarly Piccagnoni[15] found only one case in 14,000 autopsy cases.

*As pointed out by Kelly and Cullen[14] the term "myoma" has, in the case of the uterus, been used to include all fibromyomas, since pure myomas or pure fibromas are rarely if ever encountered. It is with this connotation that we use the term "myoma" in connection with fibroid neoplasms of the vagina.

TABLE I. TABULATION OF CASES

CASE	GYNEC. PATH. NO.	RACE	AGE	CIVIL STATUS	PARA.	POSITION	SIZE	SHAPE	CONSISTENCY	MUCOSA	UTERUS
1	353 (Autopsy)	C.	38	M.	0	Post. wall	4 × 2 cm.	–	–	–	Multiple "large" myomas
2	2597	W.	41	M.	ii	Post. to cervix	Small	–	"Hard"	–	Normal
3	8259	W.	45	M.	–	–	Small	–	"Hard"	Intact	Normal
4	9070	W.	48	M.	i	Ant. wall	1½ × 1 cm.	–	–	Normal	Normal
5	9877	C.	47	M.	iii	Left lat. wall	Small	–	"Solid"	–	"Slightly enlarged"
6	14661	W.	43	M.	ii	Left lat. wall, post.	1½ cm.	Oval	"Solid"	–	Myomas of uterus (12 × 11 × 9 cm.)
7	30867	W.	39	M.	–	Ant. wall	1½ in.	–	"Firm"	–	Myomas of uterus
8	37957	W.	46	M.	–	Post. wall	"Lemon size"	Oval	"Solid"	–	Normal
9	41788	W.	43	M.	iii	Post. wall	1 × 1½ cm.	Oval	"Firm"	Normal	Myomas of uterus (8½ × 9 × 8 cm.)
10	41981	C.	42	M.	i	Ant. wall	4½ × 3½ cm.	Oval	"Firm"	Normal	Myomas of uterus (6½ × 6½ × 5 cm.)
11	45943	W.	43	M.	i	Ant. wall	3 cm.	Oval	"Firm"	Normal	Myomas of uterus
12	48736	W.	39	M.	iii	Ant. wall	2½ cm.	Oval	"Tense"	Normal	Normal

Age.—In our series of 12 cases, the average age is 44 years, the oldest being 48 and the youngest 38. In the literature, however, vaginal myomas have been reported in patients from puberty to 71 years of age.[18] The average age, as in our cases, has been found to fall into the latter part of the childbearing period. "Fibromyomas" have been reported in infants,[16, 17] but microscopic evidence of myomatous elements is lacking in these cases, and it is possible that these lesions may simply have been papillomas.

Color.—In our series, 9 of 12 cases are white, and a majority of the reported vaginal myomas in the literature have been in white women. The racial incidence of vaginal myomas, therefore, contrasts strikingly with the racial incidence of uterine myomas which are almost three times as common in colored as in white women.[14] This fact we believe to be of particular interest in relation to the problem of etiology, and it will be discussed below.

Marital Status.—All of our 12 patients were married. In the literature, however, the reported cases show that vaginal myomas occur in married and unmarried, parous and nulliparous, women, alike, and there is no evidence to indicate that these conditions influence the incidence.

Association with Uterine Myomas.—A glance at our table of patients (Table I) shows that 6 of 12 cases had uterine myoma in addition to vaginal myoma. In 5 of these the uterine condition was proved at operation and confirmed by histologic study. In the sixth case (Case 1 in Table I) the uterus was studied at autopsy. The high incidence of uterine myomas in this series of vaginal myomas is at variance with previous observations recorded in the literature. Of the 130 cases of vaginal myomas reviewed by Nürnberger,[18] only 10 were found to have associated fibroid tumors of the uterus. It is possible that uterine myomas may have been overlooked in certain of the previously reported cases.

PHYSICAL FINDINGS

Gross Appearance.—In 10 of our cases the vaginal myoma presented in the vagina as a nonpedunculated ovoid mass covered with smooth, intact mucosa and had no characteristic appearance such as would allow differentiation from a vaginal cyst, cystocele, or urethrocele. In 2 cases, the myoma was pedunculated, and these, too, were covered with normal mucosa.

In a number of reported cases, ulceration of the overlying mucosa has been noted with subsequent necrosis, purulent discharge and bleeding. In a case reported by Knauer,[3] the surface of a vaginal myoma the size of a "hen's egg" was ulcerated, necrotic, and bled easily, leading to a clinical diagnosis of carcinoma. Microscopic study after removal revealed the tumor to be a benign myoma.

Dicke[19] described a case in which the myoma protruded from the vulva and resembled a prolapsed uterus.

Size.—The vaginal myomas in our series are relatively small, varying from 1.5 cm. to 4.5 cm. in greatest diameter. These tumors may, however, reach tremendous size. Pistuddi[20] described a case with a vaginal myoma which after removal was found to weigh 1,450 Gm. Simon[21] observed a vaginal myoma the size of a "child's head," as did Hofmokl.[22] Phillips[23] recorded a case in which the removed tumor measured 5 by 3.5 inches.

Number.—In all of our cases, the lesion was a single myoma, but cases of multiple myomas in the vagina have been described. Olin and Torggler[24] reported a patient with multiple vaginal tumors which they believed to be myomas, but, according to Nürnberger,[24] the microscopic findings suggested sarcoma. In 1934 A. F. Tyler[25] reported the case of a white woman, aged 68 years, with multiple myomas of the vagina, and these were diagnosed by biopsy and microscopic study.

Site.—Myomas may develop at any point in the vaginal wall. In 5 of our cases, the tumor arose in the anterior wall, in 4 the posterior wall, and in 2 the left lateral wall. In the remaining case, information as to location was lacking. In 5 cases, the myoma was in the posterior third of the vagina, and in 5 cases the anterior third. Of this latter group 4 were in the anterior wall near the midline and superficially resembled cystocele or urethrocele. In general, more than one-half of the tumors reported have occurred in the anterior wall, and about one-fourth in the

posterior wall. Analyses of cases in which the necessary data were available have shown the distribution of sites of origin recorded in Table II.

TABLE II. DISTRIBUTION OF SITES OF ORIGIN OF VAGINAL MYOMAS

AUTHOR	NO. OF CASES	ANT. WALL PER CENT	POST. WALL PER CENT	RT. LAT. WALL PER CENT	LT. LAT. WALL PER CENT
Nürnberger[26]	90	67.8	21.1	6.7	4.4
Tourneux[1]	120	55.0	25.8	10.0	9.2
Stein[11]	11	65.0	22.5	0.0	12.5
Bennett and Ehrlich	11	45.4	36.4	0.0	18.2

Regarding the distribution of myomas in the upper and lower halves of the vagina, Nürnberger[26] found an almost equal distribution between the two: of 33 cases analyzed, 12 arose in the upper half, 15 in the lower half, and in 6 cases both halves were involved.

Consistency.—Like myomas elsewhere, vaginal myomas are most often firm in consistency. In 11 of our patients, this was true. In the other patient (Case 12 in Table I), the myoma was rather soft and a diagnosis of urethrocele was made at the time of initial examination, but six years later, when the patient was re-examined, the mass had increased in size, was tense, and was thought to be a thin-walled cyst.

Downing's case[5] presented the typical physical findings of a cystocele, and it was only during operation that the true nature of the mass was discovered. Mattson[6] had a similar case in which the myoma arose in the anterior vaginal wall, was soft, and resembled a cystocele. Cystoscopic examination, however, revealed a "hillock" instead of a "depression" at the base of the bladder, and on the basis of this observation a diagnosis of tumor of the anterior vaginal wall was made. This was confirmed at operation when the myoma was removed. Ingraham[27] described a case in which the vaginal outlet was relaxed, and, when the patient strained down, a myoma, which arose in the anterior wall of the vagina, was forced from the outlet in such a way as to simulate a cystocele.

SYMPTOMS

In cases of vaginal myoma, the development of symptoms depends on the size and location of the tumor and on the degenerative changes which may occur in the overlying mucosa as well as in the tumor itself.

Urinary.—In a considerable number of reported cases, and also in our Cases 4 and 7, the myoma lay near the urethra and, by pressure, gave rise to difficulty and frequency of urination. In one reported case,[28] complete urinary retention occurred and catheterization was necessary. In another case urinary incontinence developed.[2] In a most remarkable case described by Halban,[29] a large vaginal myoma caused obstruction of the urethra and intense dysuria with subsequent hematuria. Later pressure on one ureter resulted in hydroureter and hydronephrosis for which nephrectomy was performed before the vaginal condition was recognized.

Protruding Mass.—In our Cases 8 and 10, a protruding mass constituted the patient's chief complaint.

Symptoms Secondary to Degenerative Changes.—Ulceration of the adjacent mucosa did not occur in any of our cases. This complication has been described,[3, 8, 10, 30] however, with resulting purulent discharge and bleeding. In one case, severe hemorrhage occurred following ulceration.[30]

Rectal Symptoms.—According to Nürnberger, rectal symptoms are rare as a complication of vaginal myomas, but one such case has been reported.[31]

Dyspareunia.—Obviously when the tumors attain any considerable size, dyspareunia may occur.[8]

Symptoms Associated With Pregnancy.—In association with pregnancy, difficulty in labor has been encountered in cases with large vaginal myomas. In one unusual

case reported by Cordaro,[32] a patient with a large myoma in the vagina suffered a rupture of the uterus during the course of a prolonged labor and died.

In other cases, including our Case 12, a small vaginal myoma was known to be present throughout the course of a pregnancy, no significant increase in the size of the tumor occurred, and no difficulty in labor was encountered.

DIFFERENTIAL DIAGNOSIS

As has already been indicated, myomas of the vagina may simulate malignant tumor but more often are mistaken for urethrocele, cystocele, prolapsus uteri, vaginal cyst, and even adenomyoma of the vaginal wall. Conversely, in a case recently observed by the authors (J.H.H., Gyn. Path. No. 48488), a nontender, firm, suburethral mass of four years' duration, was thought to have been a vaginal myoma, and only at operation was the condition correctly diagnosed as a chronic suburethral abscess.

Careful pelvic examination, including cystoscopic study, when the lesion to be diagnosed is in the anterior wall, will usually suffice for preoperative study. If the various possible conditions are kept in mind by the surgeon, the correct diagnosis will become apparent at operation.

TREATMENT

In 11 of our 12 cases, surgical excision was easily carried out and gave satisfactory results. In the remaining case of our series, treatment of the vaginal tumor did not seem indicated because of another disease which shortly caused the patient's death. Difficulties may be encountered because of unusual size of the tumor, or because of its intimate relationship with adjacent structures, particularly the urethra and bladder. Müller[10] has cited a case in which the bladder was entered during the surgical removal of a myoma of the anterior vaginal wall, and a vesicovaginal fistula resulted. In an occasional case irradiation may be the treatment of choice because of the poor general condition of the patient.[25]

PATHOLOGY

The vaginal mucosa is usually free from the underlying myoma, and this was true in the cases we studied. However, compression necrosis and ulceration of the mucosa may occur. The great majority of these myomas are encapsulated, but a case of diffuse myoma of the vaginal wall has been described by Downing.[5] In our cases microscopic examination showed the tumors to be composed of fibromuscular tissue with a predominance of the muscular elements. We observed no significant hyalinization or other degenerative changes, although the various types common to uterine myomas have been described.[10, 27, 33] Also, as in uterine myomas, it is possible that secondary sarcoma formation may occur, but no convincing evidence of this change can be found in the literature.

ETIOLOGY

It has been assumed by some authors that the origin of vaginal myomas is comparable with that of uterine myomas. While the exact etiologic factors in neither are known, statistics clearly show that the uterus, of all organs in the body, has a strong diathesis for myomatous tumor formation. Kelly and Cullen[14] in a thorough study of 1,674 cases of myomas of uterus found an associated myoma of the vagina in only a single case. In the same material they found one patient with a myoma of the Fallopian tube, and 3 patients with fibroid tumors of the ovary. In this study, it was apparent that the factors which caused the development of myomas in the uterus, did not exert any similar action on other Müllerian derivatives.

The negro race has a strong tendency to uterine myoma formation, but in relation to vaginal myoma this tendency not only fails to appear, but indeed seems to be reversed. In 9,000 consecutive autopsies performed in the Johns Hopkins Hospital, there were 1,560 women past 19 years of age, and of these, 719 were

colored and 841 white. The incidence of uterine myomas in the colored patients was 28.5 per cent and in the white patients, only 10.3 per cent. In this particular series not one case of vaginal myoma was observed. In the authors' 12 cases of vaginal myoma, 9 of the patients were white and only 3 colored, while the clinical material from which these cases came is more than half colored.

While myomas of the uterus are far more common than myomas in other parts of the body, myomas of the vagina occur even less frequently than myomas in the gastrointestinal tract. Here again the high race predominance in negroes is not found. In the 9,000 autopsy cases mentioned above, there were 8 cases of myomas of the gastrointestinal tract in women, 7 of whom were white.

SUMMARY

1. Twelve cases of primary myoma of the vagina are reported, and the literature is discussed.

2. The difficulties often encountered in diagnosis are cited.

3. The incidence of myomas of the vagina, the gastrointestinal tract, and the uterus is discussed, and its bearing on the question of etiology is considered.

CONCLUSIONS

On the basis of these figures we may conclude: (1) Myomas occur in the uterus far more frequently than elsewhere in the body, being present at autopsy in almost 20 per cent of all women past 19 years of age (2) Myomas of the uterus are almost three times as common in colored as in white women. (3) Myomas of the vagina occur not only far less frequently than myomas of the uterus, but even less frequently than myomas of the gastrointestinal tract. (4) Myomas of the vagina are probably less frequent in the colored than in the white. (5) The factors, whatever they may be, which so frequently induce myoma formation in the uterus, have no more effect on the production of myomas in the vagina than on the production of the same type of tumor in the gastrointestinal tract.

Theories ascribing the origin of vaginal myomas to Gärtner's duct or other embryologic remanents, seem untenable, since it is recognized that myomas develop in all parts of the vagina. The incidence of vaginal myomas is comparable not with that in the uterus but rather with that in extragenital smooth muscle viscera, such as the gastrointestinal tract.

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PERFORATION OF THE INTESTINE AFTER X-RAY AND RADIUM THERAPY OF CANCER OF THE CERVIX

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THIS report presents the details of a case in which intestinal perforation followed radiation therapy. The unusual method of metastasis as shown at autopsy is also of interest.

On May 22, 1936, Miss J. M., aged 40 years, was first seen complaining of slightly irregular menses. There was no bleeding between the periods at any time. Her past history was essentially negative except for one induced abortion, fifteen years before, at two months.

The general physical examination was negative except for hypertension (178/100). On pelvic examination the external genitals were negative; pelvic floor was excellent; fornices were shallow; cervix was unusually hard, 3½ cm. in diameter and smooth. The uterus was in second degree retroversion, normal in size and movable; adnexa were negative. No masses, tenderness or indurations were felt. A spot of blood was noticed on the examining finger at the end of the examination. A digital rectal examination was negative.

On June 12, 1936, a diagnostic curettage was done, at which time squamous cell carcinoma of the cervix was found.

Between June 18, 1936, and July 30, 1936, there were 32 deep x-ray treatments given, through 6 portals, 2 anterior, 2 posterior, and 2 lateral, 300 r. each at 50 cm.

On Aug. 15, 1936, 7,000 mg. hours of radium were given with 1 mm. platinum screen. Ten milligrams were placed in the fundus, 20 in the endocervix, 20 in the right fornix, and 20 in the left fornix. The radium capsules in the fornices were wrapped in 1 cm. of plain gauze.

Approximately one year later she began bleeding with each stool. Cramps were more severe and were relieved with paregoric and phenobarbital. She did not lose any weight and continued her work as a saleslady.

The following February the symptoms became more acute, although the bleeding was never profuse. A barium enema was given which showed an ulcerated area in the upper sigmoid.

On April 4, 1938, she was again admitted to the hospital complaining of pain in the left lower quadrant of four months' duration, with the diagnosis of extensive carcinoma plus pyometra. On April 16, 1938, a diagnostic curettage was done. A fine probe could just be inserted into the cervix. One tablespoon of thick, gray yellow, necrotic tissue was removed. Microscopic study showed carcinoma in advanced necrosis (Fig. 1).

Following this procedure she was temporarily relieved, but on May 16, 1938, she had an acute attack of abdominal pain, became cold and clammy and died in shock, two hours later.

Autopsy.—(Dr. Leon Motyloff.) Record No. 66521, Path. No. 50300.

Following are the excerpts of the autopsy report with the essential post-mortem findings: The approach into the peritoneal cavity was difficult because of extensive adhesions between the omentum and anterior wall on one side and between omentum and pelvic organs on the other side. Greenish, purulent fluid with fecal odor filled out the spaces between the intestinal loops and the large pockets formed by the extensive adhesions.

The peritoneum of the anterior abdominal wall and the abdominal surface of the diaphragm were covered with densely seated multiple nodules reaching the size of a pea. The entire omentum was also infiltrated with the same kind of nodules. The lower portion of the omentum formed a large tumor mass of not less than 5 inches in diameter. This tumor mass was directly adherent to the uterus. The surface of the latter was entirely covered with densely seated carcinomatous nodules. The wall of the uterus was entirely destroyed by the carcinoma; it presented a mixture of tumor and scar tissue.

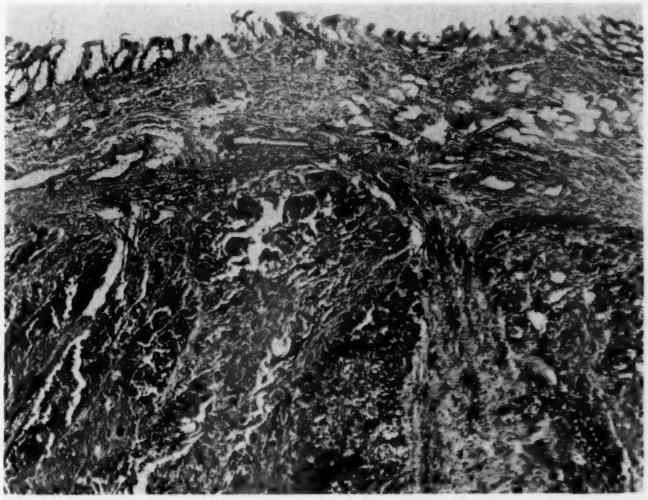

Fig. 1.

The sigmoid was adherent to the uterus and to the above-mentioned tumor of the omentum. An opening about 3 cm. in diameter with ragged edges was found in the sigmoid about 18 cm. above the anus. The perforated area of the intestine was intimately fused with the surface of the uterus. The portion of the bowel adjacent to the above-mentioned area of the perforation was infiltrated with the carcinoma. The perforated area was in free and direct communication with the above-mentioned large pockets filled with greenish fluid of fecal odor.

The soft parts of the pelvis were transformed into a necrotic tumor mass, in direct continuation with the carcinomatous nodules covering the surface of the uterus.

Following are the organs in which metastases were found: (1) Two small metastatic nodules at the lower surface and anterior edge of the lateral portion of the right lobe of the liver (superficial metastases). (2) A nodule 0.5 cm. in diameter at the apex of the left lung. The microscopic examination of the sigmoid at and in the vicinity of the perforated area revealed that the carcinoma invaded the entire wall of the intestine without actual penetration into the mucosa proper. However, the parts of the mucosal membrane which were overlying the carcinoma were entirely necrotic (Fig. 1).

The carcinoma presents everywhere a mixture of: (1) Large sheaths of flattened cells with marked hornification (Figs. 2 and 3). (2) Irregular cords of small

darkly-stained cells, which reveal a more or less cylindrical shape pointing out at the original glandular type of carcinoma (Fig. 4).

Most striking in the autopsy findings was the unusual spread of the carcinoma. The histolytic capacity of the tumor was apparently much greater than the tendency to give distant metastases. The small nodule which was found in the lung was the only evidence of distant metastatic extension of the tumor (evidently blood stream metastasis). There was no evidence of the involvement of lymphatic nodes any-

Fig. 2.

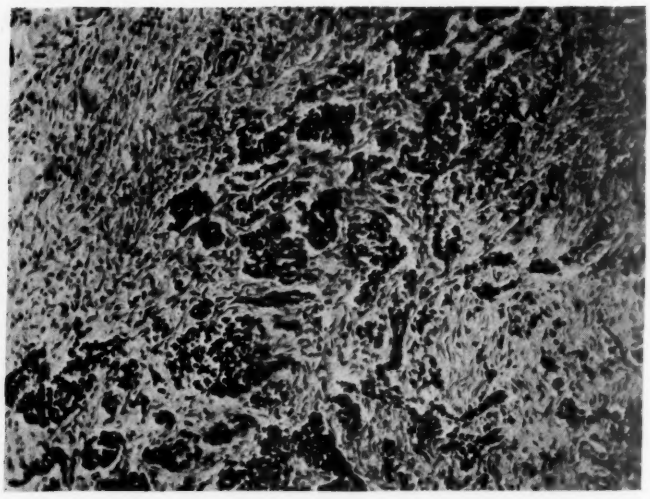

Fig. 3.

where in the abdominal or thoracic cavities. The carcinoma grew through the wall of the uterus extending from there in direct continuity into the omentum and the wall of the large bowel which were firmly adherent to the surface of the uterus. From the omentum, because of the adhesions between the latter and the anterior abdominal wall, the carcinoma involved the peritoneal covering of the abdominal wall and extended from there by direct continuity upon the abdominal surface of the diaphragm.

From the uterus the carcinoma extensively infiltrated (by direct continuity) the soft tissues of the pelvis.

The patient died of fecal peritonitis caused by perforation of the bowel.

DISCUSSION

It is thought that the concentration and proximity of the radium capsules in the vagina, without due regard to the law of inverse squares,[2] resulted in injury to the intestinal mucous membrane and with carcinomatous infiltration contributed to the perforation. The daily roentgen dose (300 r.) was perhaps high, in view of the findings of Corscaden, Kasabach and Lenz.[2]

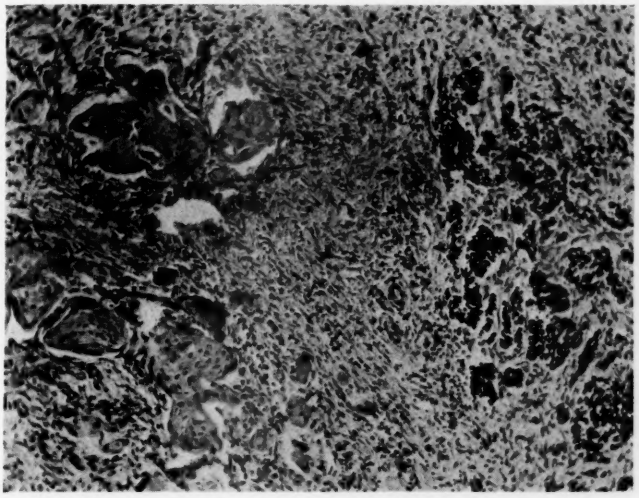

Fig. 4.

In 1935, Sackett[3] reported the complications following radiotherapy at Woman's Hospital, where smaller doses are usually given. These complications in the intestinal tract and also in the upper urinary tract were much less frequent in patients destined to survive five or ten years, than in those dying of carcinoma within five years. This suggests that the disease itself was more causative than the treatment. In his series there were no injuries like the one herein reported.

SUMMARY

1. A case report with autopsy findings following roentgen ray therapy for carcinoma of the cervix uteri is presented.

2. The importance of reducing the amount of radium in and about the cervix when the fornices are contracted is emphasized.

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SUCCESSFUL USE OF PROGESTERONE IN A CASE OF REPEATED SPONTANEOUS ABORTION

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C. G. D., a 36-year-old, Russian Jewish housewife, Bronx Hospital No. 109937, married twelve years, complained of inability to carry her pregnancies to term.

There was no familial history of hereditary illnesses, sterility, or habitual abortion. Both the patient and her husband have siblings married and with children. One of the patient's sisters has 12 children. The patient's past history was noncontributory, except for typhoid fever and pertussis and for the privations she suffered during and after the First World War in Europe. The menarche occurred at the age of sixteen; the periods lasted from one to two days and the flow was slight. Until her marriage, the patient experienced severe dysmenorrhea. Venereal diseases were denied by name, symptoms, and laboratory tests.

The patient was married in the United States in June, 1927. She and her husband were well-matched emotionally and intellectually and were anxious to have children. The patient's first spontaneous abortion occurred in August, 1927, after one missed menstrual period. In November of the same year there followed another spontaneous abortion at three months. It was suggested that "straightening the womb" would aid pregnancy; this was done without external scars in February, 1928. The operation was futile, however, as the patient again aborted spontaneously in August, 1928, at three months.

For the next few months the patient attended an outpatient department, where she says that many tests, including the Huhner and Rubin tests, were done, with normal results. By this time, the lack of a child in the family had become the source of much marital bickering and discussion as to which partner was at fault. In fact, there were a number of temporary separations.

The patient became pregnant again in the spring of 1929. She spent the next five months in bed, as near to complete rest as possible. In October she aborted twins. There was a septic postabortal course, for which a curettage was performed. She developed a severe urinary infection and was under treatment for the remainder of the year in another outpatient department.

An abortion in the second month occurred in October, 1931, following which a curettage was done. January, 1932, brought a two-and-one-half-month abortion. In September, 1932, after a long period of bed rest, the patient aborted six month twins. And finally in May, 1935, there was an abortion at three months.

The writers were consulted in June, 1939. At that time the emotional and psychologic marital disturbances were marked. The patient had been told by other physicians that persistence in attempts to bear children would be futile and even dangerous. The general physical examination was essentially negative. The patient was obese, weighing 160 pounds and measuring 60¾ inches in height. Her uterus was retroverted and the cervix small. In the absence of any serious pathologic conditions and because of the urgent desire for a child, the patient was told that she might become pregnant at any time and was advised to take wheat germ oil capsules and to rest in bed as much as possible. She had a scant period in July; early in September a Friedman test confirmed the diagnosis of pregnancy.

At the end of September, exactly three months after the last menstrual period, the patient called us in because of vaginal hemorrhage and intermittent backache. Vaginal examination was not performed. An initial dose of one international unit of progesterone was given immediately, followed by one-half unit dose twice weekly.

The vaginal bleeding quickly decreased and stopped altogether at the end of the week. The one-half unit dose was continued semiweekly for eighteen injections, after which one unit weekly was administered until the last month of pregnancy. At four-week intervals, corresponding to the time when the regular menstrual period would have come, an added injection was given in the middle of the week.

The patient continued to rest in bed. She took wheat germ oil capsules three times a day and occasional half grain phenobarbital and calcium lactate tablets, and observed a 1500 c.c. fluid salt-poor diet. Under this regime, gestation proceeded satisfactorily. The patient volunteered that she had never felt so well in her previous pregnancies as in this one. In other pregnancies she had suffered dysmenorrhea-like pain; now she felt quiet and perfectly relaxed. The blood pressure and urinalyses remained normal. The Wassermann test was negative. Fetal life was felt in November; the fetal heart was first heard in January, 1940.

Mild toxemia symptoms, slight edema and a faint trace of albumin, were noticed in March; restriction of fluids and salt was enforced. A troublesome hemangioma developed on the left thumb. Despite cauterization, it bled considerably, and irradiation was required in the post-partum period.

On April 8, 1940, the patient began to pass large amounts of amniotic fluid. She was admitted to the Bronx Hospital, and the drainage ceased after five days. She spent the last month of pregnancy in bed at the hospital; during this time no endocrine preparations were given.

The membranes ruptured and labor started spontaneously on May 7. Roentgenograms revealed the pelvis to be ample and the baby of normal size. Little progress, however, was noted. The cervix was thick and hard and did not dilate beyond two fingers. The head, which was in the left occiput posterior position, did not engage. Because of these indications, a low cervical cesarean section was performed on May 8, after a trial labor of twenty-four hours; a normal 6 pound 8 ounce girl was delivered. The mother's blood count on the day of delivery was: red blood cells 3.90 M., hemoglobin 9.6 Gm., or 66 per cent (Sahli), white blood cells 12,800; differential: polymorphonuclears 89 per cent, stab cells 1 per cent, lymphocytes 7 per cent, monocytes 3 per cent. The postoperative course was uneventful. On the day of discharge, May 22, fourteen days after birth, the baby weighed 6 pounds 14 ounces.

Within the reappearance of menstruation four months post partum, a bizarre sequel of the hormone injections manifested itself. The arms and buttocks, the sites of injection, became swollen, painful, tender, and hemorrhagic for the duration of the menstrual period. Up to the present writing, this has recurred four times.

The reaction at the sites of injection of the hormone, coincident with the menses, is probably a sensitization phenomenon. In our study of reported cases, we have found no mention of such a sequel to progesterone therapy.

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Guggisberg, H.: Significance and Prevention of Congenital Struma, Arch. f. Gynäk. **167:** 622, 1938.

The pathology of congenital struma is described at length and its relationship to maternal hypothyroidism and endemic goiter is discussed. In 1925, 53 per cent of babies born at the Bern Frauenklinik showed evidences of struma. The administration of iodine to the pregnant women throughout pregnancy during 1937 resulted in a reduction to 30 per cent. This reduction in congenital goiter depends solely upon iodine administration and is not related to maternal health. The author believes that endemic goiter could finally be eradicated and cretinism reduced to a minimum if iodine administration is continued not only throughout intrauterine life but also during childhood and maturity in order that a second generation may thus be produced under iodine therapy.

Ralph A. Reis.

MORBIDITY FOLLOWING VAGINAL EXAMINATIONS DURING LABOR

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THE controversy over the relative merits of vaginal and rectal examinations during labor has apparently quieted down. Most teaching centers seem to have decided that rectal examinations are safer and, accordingly, many students are instilled with an abnormal fear of the vaginal canal which is unreasonable and acts as a barrier when "watchful expectancy" has outrun its usefulness.

In 1925 Mayes,[1] who employs vaginal examinations, instituted a technique of vaginal antisepsis with mercurochrome, and in 1929[2] reported a morbidity of 7.3 per cent in 8,900 cases. This or a similar technique has even been instituted as a method of "sterilizing" the operative field, in certain centers advocating rectal examinations. All varieties of "vaginal antisepsis" have come into favor, from simple instillations of antiseptic solutions with a syringe, to the elaborate compressed air machines for spreading the solution over the surface of the vagina. As a rule, the instillations are done at set intervals of time during labor and after examinations.

At the Millard Fillmore Hospital we do vaginal examinations almost exclusively. We do not employ vaginal instillations in most cases, agreeing with DeLee that it is not essential to successful obstetric practice. We cannot understand why, if rectal examinations are done for the purpose of avoiding possible contamination of the birth canal, one would deliberately invade that passage to spray some colored antiseptic fluid over its surface if the advantages derived from vaginal examinations are not obtained at the same time. We are not convinced that the repeated rubbing of the vaginal mucous membrane into the cervix from the rectum is safer than a vaginal examination, and we know that for purposes of identification of the dilatation and effacement of the cervix, presentation or prolapse of the cord, position of the fetus etc., vaginal examinations are definitely superior. All too frequently the belief that rectal examinations are without danger leads to far too many being done, and precaution against placing the thumb in the introitus is often neglected. Also the findings are frequently misleading, necessitating a vaginal examination for verification, or are definitely false. Many times we have seen a patient diagnosed by rectal examination as being ready for delivery, brought into the delivery room, put under an anesthetic, and then found to have a thin but practically undilated cervix. It is embarrassing to have to return such a patient to bed undelivered, but it is far wiser than to attempt delivery at this time, which is unfortunately sometimes done.

TECHNIQUE

Our routine on the maternity floor of the Millard Fillmore Hospital, a general hospital of 261 beds, where in 1940 there were 1,844 deliveries with 155 different operators, is the following: When the labor patient is admitted, she is immediately put to bed and the vulva is shaved, using only enough green soap and water to form a lather, thus minimizing the possibility of infected material entering the vagina. This is our only preparation before the patient is taken to the delivery room. When a vaginal examination is to be done, the obstetrician puts on a sterile glove, separates the labia with the fingers of the other hand, and then, using liquid green soap as a lubricant, gently inserts two fingers and makes his diagnosis. A sterile pad is then put over the vulva. When the patient is ready, she is taken to the delivery room where a nurse gently scrubs the vulva and surrounding area with green soap followed by sterile water, six perineal pads being used for this purpose. A sponge is then put over the rectum, the physician catheterizes the patient and, using green soap freely as a lubricant, confirms the position and proceeds with the delivery. We consider the free use of liquid green soap by the operator as very important. We have had no known aspirational green soap pneumonias, although Titus warns of this possibility.

However, the proof of the effectiveness of any method is in the results. When we talk about rectal or vaginal examinations during labor being "safer," we mean that they are followed by lower maternal mortality and less morbidity. In accord with Ziegler's[3] classification of morbidity, we have separated our cases into three groups:

Afebrile: No temperature over 99° F.

Zone 1: 99.2° to 100.2° F. in any two consecutive twenty-four-hour periods, excluding the first twenty-four hours following delivery.

Zone 2: 100.4° F. and over in any two consecutive twenty-four-hour periods, excluding the first twenty-four hours following delivery.

Temperatures are taken every four hours for the first five days following delivery per vaginam, for the first seven days following section, and then twice a day thereafter, unless there is an elevation.

RESULTS

For the purpose of this study the last 1,000 consecutive deliveries were analyzed, beginning Sept. 3, 1940, and ending March 13, 1941. Since this period takes in late summer, fall, and winter, and a period during which there was a mild influenza epidemic in Buffalo, we consider it a fair criterion of our methods. Only patients five and one-half months pregnant or over are accepted on the maternity floor. Of course, with so many operators, there are a few who employ vaginal instillations and an occasional operator who does rectal examinations. Their results, though listed separately in the tables, are too few in number to justify comparison.

In this series of 1,000 consecutive cases there was no maternal death. The gross fetal mortality was 4.7 per cent and the corrected mortality 2.7 per cent. Service cases accounted for 4.6 per cent of the series.

In Table I is shown the gross morbidity, which was 4.5 per cent in the second febrile zone. It is significant that 19 of these 45 febrile cases were cesarean sections, so that the gross morbidity for deliveries per vaginam was only 2.8 per cent.

In Table II the series is analyzed according to the various methods of delivery, with their respective morbidities. Multiple pregnancies, of which there were 9, have been classified as the most difficult procedure employed for the delivery of either infant. Only 25 per cent of the cases were spontaneous deliveries. It is significant that the morbidity increases with the degree of operative interference, except in the case of versions which are performed almost entirely by a selected group of operators.

TABLE I. GROSS MORBIDITY IN PERCENTAGE

	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.
All cases	100.0	72.9	22.6	4.5
Private cases	95.4	73.0	22.5	4.5
Service cases	4.6	71.7	23.9	4.4
Deliveries per vaginam	93.9	75.6	21.6	2.8

TABLE II. MORBIDITY PERCENTAGE ACCORDING TO METHOD OF DELIVERY

METHOD OF DELIVERY	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.-
Spontaneous	25.0	82.0	17.2	0.8
Version and extraction	12.4	74.2	23.4	2.4
Breech extraction	4.0	82.5	15.0	2.5
Low forceps	48.2	73.5	23.2	3.3
Midforceps	4.2	61.9	31.0	7.1
High forceps	0.1	–	–	100.0
Cesarean sections	6.1	31.1	37.8	31.1
High classical	4.6	32.6	32.6	34.8
Low classical	0.5	80.0	–	20.0
Cervical	0.7	42.9	42.9	14.2
Porro	0.3	33.3	33.3	33.3

Table III shows the morbidity in terms of the kind of examination done, and also when vaginal instillations were employed. As stated above, there are too few of other than vaginal examinations for a just comparison.

TABLE III. MORBIDITY PERCENTAGE FOR METHODS OF EXAMINATION

	PER CENT OF CASES	AFEBRILE 98.6°-99° F.	FIRST FEBRILE 99.2°-100.2° F.	SECOND FEBRILE 100.4° F.
Vaginal examinations only	87.8	73.6	21.9	4.5
Rectal examinations only	2.5	72.0	24.0	4.0
Both vaginal and rectal examinations	2.7	81.5	18.5	–
Vaginal instillations employed	7.0	64.3	30.0	5.7

The average number of vaginal examinations per patient was 1.4. This is a very conservative estimate, for unfortunately many examinations are done which are not recorded on the chart, and some doctors examine their patients in the office before sending them to the hospital. We have not been able to demonstrate any direct correlation between the number of examinations done and the morbidity. However, when cesarean sections are excluded, it is seen by the figures in parentheses that the morbidity following none, one, and two vaginal examinations is about the same, and then the morbidity rate begins to rise, especially with an increase in the number of examinations above five.

Most patients remain ten to twelve days in the hospital following delivery, whether by normal or cesarean route. Only 16 of the 1,000 patients in this series remained fourteen days or longer post partum. Half of these were afebrile. Of the 4 remaining seventeen days or more, one had pyelitis, one was operated upon on the eighth day post partum for an ovarian cyst, with a resulting morbidity for two days, one was an afebrile cardiac, and the last had a third degree laceration and was in the first febrile zone for four days only.

TABLE IV. RELATION OF NUMBER OF EXAMINATIONS TO MORBIDITY

NUMBER OF VAGINAL EXAMINATIONS	NUMBER OF CASES	% AFEBRILE 98.6°-99° F.	% 1ST FEBRILE 99.2°-100.2° F.	% 2ND FEBRILE 100.4° F.-
0	283 (239)*	70.0 (77.0)*	22.6 (20.1)*	7.4 (2.9)*
1	341 (337)*	75.4 (76.2)*	21.7 (21.4)*	2.9 (2.4)*
2	190 (187)*	77.9 (78.1)*	19.5 (19.8)*	2.6 (2.1)*
3-5	150 (146)*	49.3 (49.4)*	46.7 (46.5)*	4.0 (4.1)*
Over 5	11 (9)*	63.6 (66.7)*	18.2 (22.2)*	18.2 (11.1)*

*Excluding cesarean sections.

SUMMARY

We are reporting a series of 1,000 consecutive cases delivered on the maternity floor of a general hospital. There were no maternal deaths and the corrected fetal mortality rate was 2.7 per cent. Seventy-five per cent of the deliveries were operative. Vaginal examinations alone or vaginal and rectal examinations were done in 97.5 per cent of the cases. Vaginal instillations were employed in 7 per cent. The gross morbidity for all deliveries was 4.5 per cent for the second febrile zone, and 22.6 per cent for the first febrile zone. Excluding sections, the respective morbidities were 2.8 per cent and 21.6 per cent. Following delivery, 1.6 per cent of the patients remained fourteen days or over in the hospital and half of these were afebrile.

CONCLUSIONS

1. Vaginal examinations during labor, when done carefully and not too often, are safe, and we believe the procedure of choice.
2. Vaginal instillations at intervals during labor and following examinations are not essential to safe obstetrics and impress us as tending toward "meddlesome interference."

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Bleyer, A.: Rôle of Advancing Maternal Age in Causing Achondroplasia, Am. J. Dis. Child. **58**: 994, 1939.

In an attempt to determine the effect of maternal age as cause of achondroplasia, Bleyer found only 47 cases in a review of the literature in which the age was mentioned or could be obtained from the author. Sending letters to heads of pediatric and orthopedic departments of many schools and hospitals in this country and Canada, he obtained data on 256 additional cases. As with mongolism, the influence of maternal age in cases of achondroplasia appears to start at or soon after the beginning of the reproductive period and increases steadily to its end. Therefore, it seems that the risk of bearing a child with either of these anomalies increases, if only by a little, with the passing of each menstruation. "Advancing" rather than "advanced" maternal age is the term to be preferred in designating this factor. Whether in these situations maternal age is in itself a cause of the defects or whether it is coincidental with another factor, as yet undetermined, is of course unknown.

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PROLAPSE OF THE PLACENTA

Report of Two Cases With Delivery of Live Babies

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PROLAPSE of the placenta is an infrequent complication of labor that rarely is reported. In the past twenty years, it has been presented in the medical literature only eight times. The last report in the English language was published by Rucker[1] in 1926. The incidence of this complication has been variously reported by different authors. It is reported to range from one case in 7,000 (Münchmayer[2]) to one case in 45,999 (Genter[3]). Sir James Y. Simpson,[4] in his memoirs, collected 141 cases, 56 being on record and the remainder from notes furnished by colleagues. Genter[3] reported 29 cases from the literature during the period of 1852 and 1913. Burczak[5] in the latest and most complete discussion of this complication gathered 46 cases from the literature and drew certain conclusions from their analysis. We have observed the following two cases during the past three years.

Case 1.—M. D., white, aged 36 years, gravida viii, para vii, was admitted to the Michael Reese Hospital Prenatal Clinic on April 12, 1937. Her last menstrual period was July 20, 1936 and she was expected to be due on April 27, 1937. Her pelvis was considered to be adequate, and her blood pressure was normal. The position of the baby was R.O.T. and the fetal head was floating. She was seen one week later at the clinic without any abnormal findings. On April 27, 1937, at 2:10 A.M., she was admitted to the hospital (service of Dr. Julius E. Lackner) in good condition. Her pains were weak and she had a slight "bloody show." This "show" soon became more prominent and at 8:40 A.M., the bleeding was bright red and large in amount according to the nurse's record. Her condition was very good. The blood count was 3,750,000 red count and 70-80 per cent hemoglobin (Tallqvist). At 10:30 A.M., a vaginal examination was performed with all preparedness available to cope with any bleeding that might ensue from the manipulation. A placenta previa lateralis over the posterior cervical lip was felt. Bleeding followed this examination and an 8 cm. intraovular bag was immediately inserted. A one-pound traction weight was added. The patient's condition was still very good. Donors were called and three were found compatible. At 1:01 P.M., or two and one-half hours after its insertion, the bag was expelled spontaneously. It was followed by a moderate amount of bright red vaginal bleeding. The patient was set up immediately and a vaginal examination showed the cervix to be 7 cm. dilated. A Braxton Hicks' version was begun at 1:25 P.M. (by A. J. K.) and the foot was brought down in two minutes. The placenta was expelled spontaneously as the foot was brought out. The baby was permitted to come through the cervix with gentle traction and with no intention to do an immediate extraction. When the head was button-holed by the cervix there was no further traction applied to the baby. The latter was not expected to survive. The face had passed the cervix which was firmly around the crown of the head. The perineum was retracted by the hand to allow air to reach the baby's mouth. The head gradually passed the cervix, aided by pressure of the assistant's hand above the symphysis. The baby, moderately asphyxiated, weighing 3,250 Gm. (7 pounds 2½ ounces), was born nine minutes after the delivery of the placenta. The uterus was immediately packed tightly. Ten minutes later the patient went into profound shock. She was given a transfusion without any delay because the donors had been kept available in the corridor outside the delivery room. She was given 550 c.c. of whole blood and 1,000 c.c. of 5 per cent glucose. The red

count at this time was 1,800,000 and the hemoglobin 50-60 per cent. Two days later a second transfusion was given to the patient and she gradually improved. Both mother and baby left the hospital thirteen days later.

CASE 2.—W. H., a 23-year-old colored female, para iii, gravida iv, had her last menstrual period on Dec. 24, 1938, and she was calculated to be at term on Oct. 1, 1939. Her previous pregnancies had terminated uneventfully with a normal puerperium each time. Her children weighed from 5½ to 7 pounds at birth. Her prenatal course was normal although she did not present herself at the clinic until the seventh month. Her blood pressure and urine were normal, the Kahn test was negative, and the vaginal smear showed no gonococci. There was no history of bleeding at any time.

On Aug. 25, 1939, at 1:50 A.M., she was admitted to the Obstetrical Ward of the Cook County Hospital (Service of Dr. Daro), having been in active labor for one hour and fifty minutes. The cervix was completely dilated on admission to the ward; the membranes were intact; the station of the head was plus two and the fetal heart tones were 132. The abdomen appeared large for the stage of gestation. She was immediately prepared and draped for delivery.

Five minutes after admission, the membranes ruptured spontaneously, the fetal head followed and was delivered within the next few pains. The delivery was complete at 2:00 A.M. The cord was cut and clamped. The mass remained in the abdomen with its ovoid in the transverse. Fetal heart tones were noted, thereby establishing a diagnosis of twins. A vaginal examination was made by one of us (P. J. S.) to determine position and presentation but only a rapidly prolapsing bag of waters was felt. This followed the hand out of the vagina and ruptured spontaneously at 2:11 A.M. The hand was reinserted only to find a soft rapidly prolapsing mass of tissue. As the examiner's hand was again withdrawn a mass fell out of the vagina which proved to be the fused double placenta. The second cord was double clamped and cut. Internal examination revealed the position to be left scapula anterior. The operator grasped the lower foot and completed a version and extraction with moderate ease. Blood clots approximating 50 c.c. were expelled immediately after the baby. The latter was easily revived with a tracheal catheter and warm baths. The first twin was a male infant weighing four pounds five ounces; the second was a female weighing four pounds two ounces. Aside from small hard old white infarcts up to 2 mm. in diameter on the maternal surface, the placenta was normal. The shortest distance from the edge of the placenta to the site of rupture of the membranes was 15 cm. A double amnion and chorion were present.

DISCUSSION

This condition virtually represents a reversal in the order of the second and third stages of labor, the placenta being expelled before the fetus. The exact etiology of this condition is unknown. It almost always occurs in multipara. It frequently occurs in premature labors. Burczak[5] in 46 cases found the following relationship to term deliveries; 16 were full term, 10 occurred in the ninth lunar month, 12 were earlier than this, while in eight instances the period of uterogestation was not determined. The same author states that the etiologic factors of prolapse of the placenta are the same as those for ablatio placentae. Thus it may be related to the toxemias of pregnancy and hypertensive vascular disease. This was evident in the case report of Mulder[6] whose patient was nephritic with high blood pressure, and she also had a narrow pelvis and a highly placed fetal head. She developed an ablatio placentae with later prolapse of the placenta. This combination is also related to placenta previa which was present in Case 1 of our series, and was reported also by Nadler.[7] Münchmayer,[8] however, states that placenta previa should not be listed among the causes of prolapse of the placenta, because, she maintains, there must be a normal implantation to start with. Rucker[1] and deVink[9] disagree with this. Multiple pregnancy, transverse presentation, hydramnios, and narrow pelves are also very important etiologic factors. Prolapse also occurs during attempts at version, especially with an associated placenta previa. (Nadler and our Case 1.)

The pathogenesis of this accident of labor depends upon the site of implantation of the placenta and upon the existence of one or more of various mechanical factors. When the placenta is placed over or near the dilating cervical os, it is logical that detachment may occur as the cervix dilates. If the head remains high, prolapse of the placenta is more likely. When, however, the site of nidation is higher in the uterine segment or the placenta is normally implanted, some other factor or combination of factors must come into play. deVink[9] postulates that there is a deficiency of the trophoblast and the decidua which allows for beginning separation. This author also considers other possible factors may be endometritis of the decidua with degeneration of the placental site, toxemias of pregnancy with infarctions of the placenta and possibly some hormonal upset. Other things which have been considered are heart disease, tuberculosis, syphilis, and severe nutritional diseases. At any rate toward the end of pregnancy, something happens which causes a tear in the spongy layer of the decidua. After this happens, some traumatic or mechanical factor takes place to complete the picture. This factor is usually something that will cause a change of the intrauterine pressure or uterine volume so as to allow separation of the contracting uterus from the noncontracting placenta. Such things may be: delivery of the first baby in multiple pregnancies (Barrelet[10] and Case 2 reported herein), sudden rupture of the membranes in hydramnios short umbilical cord, trauma to the abdomen, or intrauterine manipulation. A final factor which allows prolapse to occur is failure of a presenting part to adapt itself to the cervix so that the os is not blocked. Thus transverse presentation, a narrow pelvis with a high riding fetal head or certain monstrosities favor such a phenomenon (Larisch[11] and Miklós[12]).

Surprisingly, the clinical picture is much less acute than in abruptio placentae. Unless prolapse of the placenta occurs as a complication of placenta previa, bleeding during pregnancy is rare. Usually the patient is a multipara and has a normal course during pregnancy. The placenta loosens during labor without notice. The bleeding is frequently minimal or it may be entirely absent. Occasionally some severe bleeding may occur, and rarely does collapse ensue. In 40 of the cases reported by Burczak,[5] 12 patients had no bleeding, 15 had slight bleeding, and in only 13 was the bleeding severe after rupture of the membranes. Simpson[4] emphasized the fact that hemorrhage ceased when the placenta was entirely detached and even advocated the artificial extraction of the placenta in certain cases of placenta previa. This lack of bleeding has been explained by deVink[9] as due to deficiency of formation of decidua. When some mechanical factor ensues causing easy separation of the placenta, the bleeding is minimal because the spongiosa is degenerated and its blood vessels are closed. The uterus contracting after separation of the placenta also aids in effectively controlling the hemorrhage. Later, there may be danger of uterine atony with associated hemorrhage. The location of the placenta is sometimes difficult to determine. In order to decide whether the placenta was originally in a normal location, Larisch postulated the following rules: (1) no placenta felt on vaginal examination, (2) no bleeding before labor was well advanced, (3) free blood above the child, (4) the opening in the membranes some distance from the placenta, and (5) no trauma to the placenta. These requisites are complied with in our Case 2 reported herein.

The prognosis for the child is bad. In Burczak's[5] 46 cases, there were only 5 live births. Delivery must follow very soon after prolapse of the placenta. This, of course, depends on the promptness of action of the operator and on the dilatation of the cervix. If at the time of the unexpected occurrence of this accident, both the mother and the accoucheur are prepared for an immediate delivery, a live child is more likely to be obtained. This fortunate coincidence accounts for the delivery of live babies in our cases. The danger to the mother lies in atony of the uterus with hemorrhage when the placenta is separated or expelled. Considering the general mortality of certain of the etiologic factors, such as placenta previa, or ablatio placentae, that of prolapse of the placenta is not high. Various mortality reports of prolapse range from 1 death out of 15 to 10 out of 46 (Burczak[5]). There is also danger of infection along the umbilical cord to the placental site.

SUMMARY

1. Two cases of prolapse of the placenta with delivery of live babies are presented and the literature is discussed.

2. This complication most frequently occurs in multiparae and in premature labors. It is associated with placenta previa, ablatio placentae and toxemias of pregnancy.

3. Prolapse of the placenta is favored by the following factors: The first, initiating separation; then, some mechanical factor causing a sudden change in intrauterine pressure, and last, an uncovered cervical os permitting free extrusion of the placenta. Clinical examples of these factors were enumerated.

4. The symptomatology is frequently benign. Hemorrhage, fortunately, is not marked. In typical cases, the placenta has a normal implantation. However, placenta previa may be complicated by this phenomenon.

5. The prognosis for the infant is extremely unfavorable, while for the mother, the outlook is surprisingly better.

6. If feasible, immediate delivery from below, usually by version and extraction, is the treatment of choice.

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ACUTE RHEUMATIC FEVER COMPLICATING ADVANCED PREGNANCY

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ACUTE rheumatic fever complicating advanced pregnancy is of such rare occurrence as to warrant individual case reports.

Bramwell and Longson,[1] in a review of their experience with 350 obstetric cardiacs, state, "We have not yet met with any case of acute articular rheumatism or of acute rheumatic carditis during pregnancy." Similar observations have been made by MacKenzie[2] and by Jensen.[3]

Schaeffer,[4] in 1886, reported a case of a 35-year-old gravida v who developed acute rheumatic polyarthritis four days before the onset of labor. She was treated with salicylates and immobilization, and was delivered normally of an apparently healthy baby. Heffernan[5] described a 25-year-old primipara who, during the eighth month of pregnancy, developed acute rheumatic fever. Despite the liberal use of salicylates, the condition grew worse and after three weeks of conservative treatment, labor was induced and delivery effected. "The remarkable feature of the case was the rapid response to antirheumatic treatment when the uterus was emptied.[5]" Hamilton, summating his experience of 850 cardiac obstetric patients, states that "in only seven instances have we been tempted to diagnose active rheumatic disease in a

pregnant woman. These were mild affairs. . . . It has been a constant surprise to us to see evidence of activity fail to appear.[6]''

As the reports of similar experiences are so few, it seems desirable to report the following case.

CASE REPORT

E. D., a white, American, 29-year-old, married, para 0, gravida i, was admitted to Kings County Hospital on the service of Dr. Charles A. Gordon on May 7, 1940 from the cardiac obstetric clinic. The patient suffered from an original attack of rheumatic fever at the age of 4 years, with one recurrence at the age of 14. Acute osteomyelitis of the left leg occurred at 22 years of age but left no sequelae. The ante-partum course had been uneventful except for a brief episode of acute bronchitis for which she had been hospitalized and which cleared rapidly on bed rest alone. Admission had been advised as all cardiac patients are routinely hospitalized for rest at least two weeks prior to their expected date of confinement. The last menstrual period was Aug. 23, 1939, and the calculated date of confinement May 30, 1940.

Physical examination of the patient on admission revealed a young, well-developed woman who did not appear ill. The temperature was 99.2° F., the pulse 108, the respirations 24, and the blood pressure 124/94. Regular sinus rhythm was present. The heart was enlarged beyond the mid-clavicular line, the apex impulse being in the sixth interspace. Presystolic and systolic murmurs were heard at the apex. The second sound at the pulmonic area was accentuated. The lungs were clear. Obstetric examination revealed a normal pregnancy at term. She was not in labor. *Laboratory data:* The urine was negative. The blood count was 3.4 million red cells, 7,200 leucocytes with 76 per cent polymorphonuclear leucocytes and 64 per cent hemoglobin.

On the day following admission, the temperature, pulse and respiratory rate returned to normal and remained so until May 12 (six days after admission), during which time she had no symptoms. On this date, the temperature began to rise, reaching 99.2° F., accompanied by an increase in the pulse rate to 90. This continued the following day and was associated with a mild gastrointestinal upset, manifested by nausea, vomiting, and anorexia. At this time, the urine contained acetone but no diacetic acid. Vomiting ceased twenty-four hours later and the acetone disappeared from the urine. The status remained unchanged until May 15, when for the first time, she complained of pain in the left sacroiliac, shoulder and elbow joints. No redness or swelling was apparent, but these articulations were tender to palpation. The temperature at this time ranged between 100.6° and 101.8° F. with a pulse rate of 96 to 106. The blood count was 4.37 million red blood cells, 12,300 white blood cells with 79 per cent polymorphonuclear leucocytes and the hemoglobin 67 per cent. The sedimentation rate was 24 mm. in thirty-five minutes. An electrocardiogram revealed sinus tachycardia. Sodium salicylate with sodium bicarbonate was administered in doses of gr. xx three times daily but failed to alleviate the symptoms or to affect the temperature and pulse rate. The dosage was, therefore, increased to gr. xxx, t.i.d., also without effect, while further increase in dosage caused salicylism. On May 17, a musical, systolic, gruntlike murmur was heard at the fourth interspace, just to the left of the sternum. Next day, the pain in the joints had decreased considerably but the left wrist became involved and was excruciatingly painful. At this time the blood count was 3.12 million red cells, 10,000 white cells with 80 per cent polymorphonuclear leucocytes and the hemoglobin 64 per cent. An electrocardiogram showed only sinus tachycardia. The temperature on this day declined to 98.8° F. but the pulse rate remained at its previous level. Within the next twelve hours, the original joint manifestations gradually but completely disappeared.

At 3:15 A.M. on May 19, labor started and a six-pound two-ounce, living female infant was delivered at 7:45 A.M. by prophylactic outlet forceps under novocaine anesthesia. Following delivery the temperature ranged between 99° and 101° F. for six days, returning to normal on May 25 and remained unchanged until discharge. During this period, the pulse ranged between 90 and 124. Salicylates were continued in doses of gr. xx four times daily until May 28. Repeated sedimentation rates during this interval consistently showed a fall of 24 mm. in fifteen to twenty

minutes, but on June 1, it increased to 180 minutes. The involvement of the left wrist disappeared within forty-eight hours of delivery. The murmur heard on May 17 likewise disappeared within three days after parturition. On June 1, the urine was negative, and the blood count was 3.26 million red cells, 11,100 white cells with 66 per cent polymorphonuclear leucocytes and the hemoglobin 78 per cent. Repeated blood cultures showed no growth. Thereafter the post-partum course was entirely uneventful, and she was discharged on June 13, twenty-five days post partum.

Since discharge she has been attending the cardiac clinic regularly and has experienced no diminution of cardiac reserve. The physical findings were similar to those reported on the first visit to the cardiac clinic.

Both immediately post partum and during its entire hospital stay, the baby showed no evidence of rheumatic fever or rheumatic carditis.

DISCUSSION

The reason advanced for the rarity of this complication of pregnancy is that, statistically, rheumatic fever is a disease of childhood and adolescence rather than of maturity. Hence, recurrences are less likely to take place. Hamilton[6] points out that the average age at the time of the first attack of rheumatic fever is 13½ years, whereas the average age of pregnant cardiac patients is 27 to 28 years. This is in accord with our own experience.

The occurrence of rheumatic fever in a primipara with mitral stenosis at term posed two interesting problems: its effect on the mother and baby and its effect on the management of labor. There is considerable divergence of opinion as to the effect of infection on prognosis in cardiac obstetric patients. Some feel that infection is more likely to be the final insult to a failing heart, while others state that it is the prime factor in severe failure and death. The patient described above was treated for rheumatic fever in the usual manner and labor was allowed to proceed in a normal fashion. After delivery, prolonged bed rest was given and resumption of activity was permitted only when all signs of infection had subsided, and the general physical condition warranted it.

In Schaeffer's patient,[4] as reported above, the baby developed polyarticular arthritis associated with fever, three days after birth and ran a stormy course for the next six weeks. He felt that this was due to intrauterine infection, though it seems possible that it might have contracted the disease from the mother postnatally. The other authors made no note of rheumatic infection in the child, and the baby in our case has remained healthy.

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LITHOPEDION ASSOCIATED WITH NORMAL TERM PREGNANCY AND SUBSEQUENT RUPTURED TUBAL PREGNANCY

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THIS case is reported, not only because of its rarity, but also because of its clinical interest.

C. L., a British West Indian colored female, aged 30 years, was brought by ambulance to the Sydenham Hospital on July 12, 1940. She complained of severe abdominal pain and vaginal bleeding.

On Jan. 26, 1940, five and one-half months before, the patient had given birth to a full-term, normal baby. The labor was unattended, and the post-partum course was uneventful. One month after delivery, she resumed coitus.

On May 19, 1940, four months after delivery, she experienced vaginal bleeding, which she interpreted as her first post-partum period. In June, 1940, there was scant bleeding, with clots, of two days' duration. On July 9, 1940, three days before her admission to the hospital, intermittent spotting of blood occurred. On July 11, twenty-seven hours before admission, the patient had a sudden non-radiating, lancinating pain in the right lower quadrant. This was followed by progressive abdominal enlargement. There was no fainting.

Examination following admission to the hospital revealed a well-developed, well-nourished negress, 30 years of age, who appeared acutely ill. The pulse was regular, of fair quality, with a rate of 112; the systolic blood pressure was 130 and the diastolic 92. The temperature was 99.6° F.; the respirations 24. She was apprehensive. The conjunctivas and nail beds showed marked pallor. The tongue was dry and furred.

The abdomen was distended, tender throughout, and rigid. There was marked rebound tenderness. Shifting dullness was elicited.

Gynecologic examination showed a parous introitus. The cervix was soft, not patulous, and tender on motion in all directions. The uterus could not definitely be mapped out because of the distention and rigidity. A tender mass bulged into the left half of the posterior fornix.

Blood examination showed 54 per cent hemoglobin, a white count of 12,600, and a sedimentation rate of 14. Wassermann and Kahn tests were negative. Urinalysis showed faint traces of albumin and sugar; urobilinogen was 2-plus; there were hyaline casts and a few white and red blood cells.

A diagnosis of left ruptured ectopic pregnancy was made, and the patient was prepared for immediate operation.

Upon opening the abdomen, a large quantity of blood, with fresh and old clots, was found. There was a large, hard mass wrapped in omentum and loosely adherent to the cecum. This had the appearance of a calcified parasitic fibroid. When the omentum was freed, it became evident that we were dealing with a large lithopedion. The right ovary was enlarged by the presence of a corpus luteum of pregnancy, 3 cm. in diameter. The right tube was congested, but otherwise apparently normal. The uterus was the size of a six weeks' gravidity, soft and blue. The left tube was represented by a fist-sized sac, through the posterior inferior angle of which there projected a 12 cm. sized fetus. The head was still contained within the sac. There was no evidence of a placenta in the abdominal cavity.

A left salpingo-oophorectomy was performed, the lithopedion dissected from its envelop, and the abdomen closed. The postoperative course was uneventful.

The pathologic report was as follows:

A. A resected tube. Almost the entire tube except for the distal quarter had been expanded to form a sac approximately 7 cm. in diameter. At one point the sac presented a perforation forming an opening into the lumen 2½ cm. in diameter. This led into the cavity of an amniotic sac of a placenta firmly adherent to the inside of the dilated tube. Attached to the placenta was an umbilical cord approximately 15 cm. in length. This remained attached at the other end to a well-formed and normal-appearing fetus, measuring approximately 7.5 cm. from crown to rump. The head of the fetus lay within the tube, the opening of which (described above) was about the neck of the fetus. The remainder of the fetus had passed through the perforation of the tube and lay external to the tube.

B. A fetus measuring approximately 15 cm. from crown to rump, the extremities being disposed in a typical folded manner. All the tissues had a hard, woody consistency. Numerous fibrous and fibrofatty adhesions were attached over the surface of the body. No umbilical cord was present. The right auricle was distinguishable. The facial features were masked, as if by a veil of tissue incorporated with and covering the face. The limbs were somewhat distorted and misshapen. The left foot had been amputated at the tarsus; it was present just above the left elbow where it was adherent though slightly movable.

A summary of a careful review of this patient's entire menstrual history indicated that her menstruation had commenced at the age of 13, and recurred regularly every thirty days with a moderate flow, lasting four days, without pain. Her initial sexual contact had been at the age of 26 (four years before) and the next menstrual period was three days late. With the exception of the amenorrhea during her one normal gravidity, this was the only delay recalled by the patient. There was, then, no period of amenorrhea to correspond with the intra-abdominal pregnancy, nor were there any symptoms.

In this case, there is a coincidence of a lithopedion and subsequent intrauterine pregnancy, and an extrauterine pregnancy subsequent to that, with rupture (and incidental discovery of the lithopedion). The other tube was completely normal. The lithopedion was free in the abdominal cavity, adherent to the omentum. There was no trace of placenta. We have here the coincidence of an abdominal calcified pregnancy, and intrauterine pregnancy, and extrauterine pregnancy, offering, as far as we know, a unique combination. The age of the lithopedion can only be inferred, since there are absolutely no symptoms in the history, no period of amenorrhea to correspond with a pregnancy. The date of conception of the intrauterine pregnancy which anteceded the ruptured ectopic was fourteen months before admission to the hospital. It is conceivable on the basis of time and the complete absence of any previous period of amenorrhea, that we are dealing with a combined as well as a compound pregnancy, that is, that the abdominal pregnancy and intrauterine pregnancy were simultaneous. This is a difficult thing to prove in the absence of any history of pain or untoward incident during the course of the intrauterine pregnancy, and in view, perhaps, of the degree of condensation of the lithopedion.

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MASSIVE CONDYLOMATA ACUMINATA OF THE VULVA COMPLICATING LABOR

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MASSIVE condylomata acuminata of the vulva complicating labor have rarely been reported. This unusual association was seen recently in two instances and is being reported because of the unexpected favorable response of the vulval tissues during the second stage of labor. Search through the literature has revealed only three such cases.[1-3]

Striking similarity in the clinical picture can be noted in these three cases. In each, the lesions were massive; grew rapidly during pregnancy and were widely distributed about the vulval tissues. All three patients were at term. One patient, allowed to deliver spontaneously, died of sepsis. Two were delivered by cesarean section, but in only one was the presence of the condylomas the indication for surgery.

In the one instance of spontaneous delivery,[2] an attempt was made to deliver the patient by forceps. Due to the difficulty encountered in applying the forceps, this method was abandoned, and the patient was finally allowed to deliver spontaneously. No episiotomy was performed and there were no lacerations. On the third day post partum, the patient developed a chill, and fever of 103° F. On the fifth day she died of acute peritonitis and generalized sepsis.

One patient[1] was delivered by cesarean section because of the presence of the vulval lesion. This patient ran a febrile course for forty-seven days following delivery, but eventually recovered. The condylomata acuminata were later excised.

The second patient[3] who had a cesarean section was delivered abdominally because of four previous sections and cephalopelvic disproportion. Here, the lesion was excised one month prior to delivery, and at the time of delivery the vulva was well healed. The post-partum course was uneventful.

CASE REPORTS

CASE 1.—R. C., a 16-year-old, colored nullipara, was admitted to the service of Dr. Charles A. Gordon on Dec. 9, 1939. Her last menstrual period was May 15, 1939. Four months prior to admission the patient noted a "red rash" over the entire vulva, which itched almost continuously, and was associated with a thick yellow vaginal discharge. The roughened area increased in size, and rapidly assumed the character of a dense warty growth. In November, 1939, she attended an obstetric clinic where she was given expectant and palliative treatment, but because of the rapidity of the growth she was later admitted to the hospital.

The Wassermann and gonococcal complement fixation tests were negative, although her husband was said to have had "trouble with his blood," and had received intermittent treatment. Dark-field examination of the lesion was reported as "Spirochaeta resembling pallida." A biopsy taken Nov. 2, 1939, showed dyskeratosis and hyperkeratosis. Three days after admission, the patient was transferred to another hospital for contagious diseases where she remained until Dec. 8, 1939, when she signed her release. Smears for gonococci were negative as was the Wassermann test. The lesion was diagnosed as condylomata acuminata. The following day, the patient noted an escape of fluid from the vagina and applied for admission to the Kings County Hospital.

Examination of the abdomen revealed a seven and one-half months' pregnancy. The position was L.O.A. and the head was floating. The fetal heart was normal. The vulva was covered by a dark brown, profusely distributed, foul-smelling, warty growth. The clitoris was hypertrophied, bulbous, and inflamed. Condylomas involved both labia majora, which were congested and edematous, and

extended from about 1.5 cm. from the anterior fourchette downward to the anus, which was almost encircled. The lesion was 3 cm. in thickness in its area of greatest development. The width of each labia was 2 cm. and the length 15 cm. The growths were nontender, friable, and bled easily. The labia minora were not involved (Fig. 1).

Rectal examination revealed an uneffaced, closed cervix. The vertex presented and was not engaged. The rectovaginal septum was somewhat resistant and thickened.

Labor began at 6:15 P.M. Dec. 10, 1939, one day after admission. The duration of the first stage was five hours and thirty-five minutes. Vaginal examination at this time revealed the posterior wall of the vagina to be coarse, granular, thickened, and rather inelastic, although it could be depressed somewhat. The cervix was fully dilated and the membranes intact. There was moderate resistance to the advancing head. No episiotomy was done because of the danger of infection and bleeding, which might result from the necrotic and congested tissue. The membranes began to bulge at 11:50 P.M., and were ruptured artificially. As the presenting part reached the introitus, an effort was made to control the rapidity of its

Fig. 1.—Case 1. External view of condylomatous masses.

descent. The head was allowed to stretch the vulval tissues gradually while the elasticity of these structures was observed. It was seen that the stretching of the labia and perineum was normal in all respects, and at no time did there appear to be any danger of laceration. The lesion appeared to have no significant effect on the delivery of the infant. A four-pound ten-ounce female infant was delivered at 11:58 P.M. The placenta was expelled spontaneously, intact, seven minutes later. There was no gross pathology of the placenta noted, bleeding was minimal, and there were no lacerations. Duration of labor was five hours and fifty minutes.

Following delivery, the patient's temperature fluctuated between 99.4° and 103.4° F., the highest temperature occurring on the sixth day post partum. The patient was put on a course of sulfanilamide, receiving a total dose of 15 Gm. The temperature fell to normal on the tenth day where it remained until the patient was discharged.

Following delivery, the growth reduced markedly in size, but the odor and necrotic nature persisted.

Numerous laboratory tests were done and cultures taken. These were all negative except for one uterine culture, which revealed *streptococcus hemolyticus.* Wassermann tests on two occasions were negative, as were numerous smears for gonococci.

CASE 2.—M. J., an 18-year-old, colored nullipara, was admitted to the service of Dr. Charles A. Gordon on Aug. 9, 1940. Her last menstrual period was Dec. 31, 1939. Three months prior to admission she first noted the presence of "warts" about the vulva, which progressively and rapidly increased in size. She experienced itching of the vulva and burning on urination soon after the growths were noted. Labor pains began on August 8, one day before admission.

Examination of the abdomen revealed a seven and one-half months' pregnancy. The vertex was presenting, the fetus active, and the fetal heart was normal. The labia majora were covered by three large, and other numerous smaller protruding cauliflower-like growths. Two of the large lesions occupied the lower one-half of both labia majora. The largest lesion measured 1½ by ¾ by ½ cm. The lesions were pinkish, vegetative, moderately firm, nontender, and the surface showed numerous papillae. Several small condylomas were distributed about the anus and in the fold between the thigh and labia majora on the right. The large lesion on the left extended to, and covered a part of the perineum.

The Wassermann test was negative. Vaginal smear showed many pus cells and a gram-negative diplococcus resembling the gonococcus. A biopsy of the lesion was reported as "Condylomata acuminata with subacute and chronic infection."

After twenty-two hours of labor the patient was delivered spontaneously of a four-pound eleven-ounce, living, male infant. The duration of the second stage was thirty-two minutes, and the third stage ten minutes. During the second stage, distention of the vulva and perineum progressed normally and appeared to be little affected by the lesions. The tissues involved by the growths stretched easily and did not lacerate.

The post-partum course was febrile, fever of 102.2° F. occurring on the second day post partum, and the highest temperature of 103.4° F. on the eighth and ninth days post partum. The temperature was normal on the eleventh day, and she was discharged on the twelfth. Sulfanilamide was given between August 11 and 17 (the dose grains xx every four hours). Her general condition at the time of discharge was good.

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Fifteen per cent of the inmates of the Indiana State School for the Blind have a clear history of ophthalmia neonatorum. The best way to prevent the disease is to instill a few drops of fresh 1 per cent solution of silver nitrate in the baby's eyes as soon as possible after delivery.

If pus appears in a baby's eyes, a culture and smears should be made. If the gonococcus is present, the baby should be hospitalized and if possible placed under the care of a competent ophthalmologist. A baby with ophthalmia neonatorum should never be treated at home, because the constant and skilled attention of a properly trained nurse is absolutely necessary.

Sulfanilamide in 2 gr. doses every four hours for three days has been used with good success. Foreign protein, given intramuscularly to raise both the body temperature and the antibody titer, may be used with some benefit.

In these cases minutes are precious. A day may mean the difference between sight and blindness.

J. P. GREENHILL.

OVARIAN PREGNANCY WITH LIVING CHILD AND MOTHER

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THE purpose of this paper is to report an ovarian pregnancy which went beyond term and resulted in a living baby and a living mother. According to the available literature, 38 cases of ovarian pregnancy have gone to the age of viability (seven months) or beyond. Of these 38 cases, 12 resulted in living babies and 22 resulted in living mothers. In 8 cases both mother and baby lived.

Cuthbert Lockyer (1917) in accounting for the discrepancies in accepted and reported cases of primary ovarian pregnancies up to 1909 noted that Norris (1909) adopted the English standard of excluding cases published before that of Van Tussenbroeck (1899) and explained that this standard was not followed by the German writers. The German and American estimates of the total number of ovarian pregnancies up to 1909, therefore, vary from 8 to 2.

Mrs. M. F., colored, aged 41 years, had been married twenty years and had had 4 full-term pregnancies with uncomplicated spontaneous deliveries. She had received prenatal care for this pregnancy (fifth) at The King's Daughters' Maternity Center where several medical students had recognized an abnormal enlargement of her abdomen, and in the latter part of her pregnancy had made these diagnoses: "fibroids, multiple pregnancies, placenta previa, and transverse lie." The course of this pregnancy had been symptomatically uneventful except for a small amount of vaginal bleeding on Jan. 21 and 22, 1939. Her last menstrual period was Nov. 25, 1938. Her expected date of confinement was Sept. 1, 1939; and on account of extreme abdominal enlargement and failure to begin labor, she was admitted to another hospital on Sept. 9, 1939 for observation. Following an x-ray and several days' stay in the hospital she was discharged undelivered.

On Oct. 4, 1939, I saw her for the first time when she was admitted on my obstetrical service at the Norfolk General Hospital after having been in abnormal labor for eighteen hours. On admission she was complaining of abdominal tenderness, intermittent, irregular, abdominal pain; but there was no vaginal bleeding or discharge. Abdominal examination revealed a greatly distended thin-walled abdomen, the height of the fundus to be 33 cm., and a suprapubic fullness that arose perpendicularly from the pubic bone for about 14 cm. and then extended upward toward the fundus of the uterus. The abdomen was tense and felt cystic. The tenderness was diffuse. No uterine contractions were present. The fetal head was palpable in the right iliac fossa, but due to the extreme tenderness and distention, the soft parts of the baby were indeterminate. Fetal heart sounds were heard in the left lower quadrant and over the entire lower abdomen. No vaginal examination was made. The rectal examination revealed an irregular mass high in the pelvis which had no connection with the fetal head. It was impossible to outline the cervix. External pelvimetry was that of a normal gynecoid pelvis. X-ray examination following admission showed a full-term pregnancy, head not engaged, face presentation, and brow in the right iliac fossa. The patient was prepared for immediate cesarean section with preoperative diagnosis of postmature pregnancy, face presentation, and suspected abdominal pregnancy.

The abdomen was opened by a midline incision from the pubis to the umbilicus. Upon opening the peritoneal cavity a moderate amount of brownish green fluid escaped. The nonpregnant uterus occupied the suprapubic area, extended vertically, and was about the size of a two and one-half months' gestation. A mass filled the entire abdominal cavity. Its bluish gray surface contained large tortuous veins. The wall of the tumor was found to be extremely thin when it was opened by an incision about six inches in length. A postmature normal male infant, weighing 10

pounds and 3 ounces, was removed and resuscitated with the Drinker respirator and B. and J. inhalator. As soon as the baby was removed, the sac which had contained the baby collapsed. The patient immediately went into shock. Anesthesia was stopped. Oxygen was administered along with emergency treatment of the shock before the operation could proceed. Removal of the baby permitted a more careful examination of the abdominal pathology. The uterus was in relatively normal position, about three times the normal size, and uncomplicated by adhesions. The right tube and ovary were normal. Both round ligaments were greatly hypertrophied and found in their normal locations. The gestation sac was not densely adherent to the surrounding intestines. There were several fine adhesions between the descending colon, sigmoid, and posterior surfaces of the sac. Several fine adhesions were located between the loops of the small intestines and the posterior surface of the sac. All of these adhesions were easily separated with the fingers and scissors. The sac occupied the location of the left ovary. The left ovarian ligament arose from the sac and was attached to the body of the uterus. The left tube was identified adherent to the anterior surface of the sac and intact in its entire length. The left infundibulopelvic ligament was greatly enlarged by the blood vessels which carried the main blood supply to the fetus. Many of these vessels were a centimeter in diameter. The sac was thin, not more than a few millimeters in thickness, with the placenta attached to its posterior, left, inner surface. Removal of the left adnexa was comparatively simple.

Postoperatively the patient required immediate treatment of her acute shock. She had a morbid course for two weeks. She was discharged on the nineteenth postoperative day in good condition with a living child.

The pathologist's report was as follows: "Placental sac: This is a ruptured sac which is about the size of a basketball. The placenta basalis and umbilical cord are attached to the inside of the sac. The infundibulopelvic ligament and ovarian ligament are attached to the outside. The tube can be demonstrated by inserting a hemostat through its lumen. Biopsy from sac and placenta (microscopic examination): One section shows typical chorionic villi and syncytial cells. There are small areas of coagulation necrosis. The other two sections show connective tissue in which there are bundles of smooth muscles, arterioles and venules. No ovarian tissue is demonstrable. One of the sections contains a cross-section from the isthmus of the oviduct. The lumen is small. The mucosa is folded and lined with simple columnar epithelium. The wall contains the usual smooth muscle fibers. Diagnosis: Extrauterine pregnancy, ovarian."

The follow-up examination on Nov. 14, 1939, revealed a normal multiparous pelvis except for the absence of the left adnexa and the presence of a small cystic mass in the cul-de-sac which was not tender and was believed to be a resolving hematoma.

DISCUSSION

The criteria of ovarian pregnancy as designated by Spiegelberg are: (1) The tube on the side of the pregnancy must be intact. (2) The fetal sac must occupy the position of the ovary. (3) The pregnant ovary must be connected with the uterus by the uteroovarian ligament. (4) Definite ovarian tissue must be found in the wall of the sac. This specimen grossly complied with these stipulations. Microscopically it was impossible to find ovarian tissue in any of the several pieces examined. This case bears out the statement of Norris and Mitchell:[30] "12 highly probable cases are at term, which is interesting in illustrating the greater distensibility of the ovary over the tube. . . . The great growth of the fetus destroys the relations and obliterates normal tissue to such an extent that the fulfillment of all of Spiegelberg's criteria is quite difficult." The thinning of the sac in my patient was probably the cause of failure to find the ovarian tissue.

FETUS PAPYRACEOUS

Triplet Pregnancy, With One Normal and Two Papyraceous Fetuses

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PATIENT, aged 29 years, was delivered of her first baby by one of us (O'R.) in 1938. There was nothing remarkable about her ante-partum course. She had a normal delivery of a 3,650 Gm. male child. Post-partum course was normal.

She returned in the spring of 1940 in the second month of her second pregnancy. Her general condition was good, her serology negative, and she ran a perfectly normal prenatal course. There was nothing to make one suspicious of a multiple pregnancy.

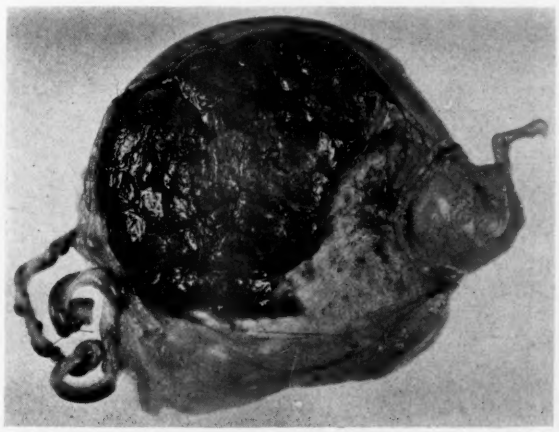

Fig. 1.—Showing second papyraceous fetus embedded in amniotic sac of normal fetus.

Three weeks before her estimated date of confinement, she went into labor. She came to the hospital where one of us (C.) found a mass protruding from the vulva. A fetus papyraceous was delivered, which apparently had died between the fourth and fifth months. The only evidence of cord was a small dried-up string-like structure. Following this delivery, the labor stopped, the cervix contracted to about 2 cm. dilatation. As the uterus did not seem very large, it was thought advisable to let the normal fetus develop further, so the following day the patient was sent home.

Nine days later, the patient returned in active labor and after eight hours was delivered of a normal 3,400 Gm. male baby.

Examination of the placenta and membranes revealed a second papyraceous fetus embedded in the amniotic sac close to the placenta. The patient made an uneventful recovery.

Dr. Herbert Traut, who made the pathologic report, said this was a biovular fetation and suggested this abnormality may be more common than generally suspected, due to the fact that papyraceous fetuses may be missed if the amniotic sac is not carefully inspected, especially if fetus dies early.

FETUS COMPRESSUS DIAGNOSED BY X-RAY

R. C. TERKUILE, M.D., AND B. M. PARMELEE, M.D., BRIDGEPORT, CONN.

AMONG the rarely noted instances of this anomaly, the case reported by Kerr and Rypins[1] is the only instance in which x-ray evidence of the presence of fetus papyraceus was obtained before delivery. In their case, the patient delivered spontaneously and expelled a compressed fetus which appeared to have approximated the age of the living child.

Fig. 1.

CASE REPORT

Mrs. G. H., a 24-year-old primipara, was admitted to the hospital at term. The diagnosis of breech presentation had been made earlier in her pregnancy, but an attempt at external version had been unsuccessful. Her past history was negative. The pelvis was of the android-gynecoid variety but was judged adequate for a baby up to 8 pounds. Labor had begun spontaneously at home with the membranes intact. Pains on admission were every five minutes, but the breech was high so a rectal examination was not done. The labor during the next twelve hours was characterized by long intervals of five- to seven-minute pains which were strong enough to have engaged the breech. A vaginal examination revealed a cervix that barely admitted two fingers and was thick and tough. The palpating fingers came against an uneven rather rough surface with tiny sharp points placed

at intervals (later found to be the rib margins of the compressed fetus). It was decided that further examination might make an abnormal situation worse and that an x-ray was in order.

A radiographic examination (Dr. Parmelee) of the abdomen shows a full-term fetus in utero in a frank breech position. In addition it was possible to identify another fetus, of approximately four months in size, lying transversely beneath the breech of the first fetus and across the cervix. The maternal pelvic development was normal and the dimensions of the pelvic inlet within normal limits except for a rather flat sacrum and, therefore, narrow posterior pelvis.

A low transverse cervical cesarean section was done under nitrous oxide-oxygen-ether anesthesia, and a normal female infant weighing 6 pounds 2 ounces was delivered. The compressed fetus was found to completely cover the internal os of the cervix much like a central placenta previa and was removed with the secundines. It possessed its own placenta and membranes, the former adhered to the margin of the normal placenta. The membranes could not be clearly differentiated and were loosely adherent to the outer margin of the right arm and leg of the compressed fetus. The cord was wrapped once about the right arm and leg. Both patient and baby are doing nicely.

There was no indication during this patient's ante-partum course of the presence of any abnormality and her general condition was excellent.

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A fortunately rare complication of criminal abortion is tetanus. A young woman three and one-half months pregnant was aborted at home by the use of sound and curette. The following day chills and fever appeared. There was a slight show of blood. Another curettage was done and ice packs were applied to the abdomen. On the seventh day after the first intervention, the patient noted pain on chewing or turning the head. General malaise, headache, and fever ensued. Three days later she could not open her mouth.

On admission to the hospital the patient was opisthotonic, with tonic and clonic convulsions. Avertin was administered per rectum and a gauze pack saturated with antitetanic serum, inserted into the uterus alongside a catheter. Through the latter 3,000 units of tetanus antitoxin were instilled hourly and irrigations of oxygenated water were given for ten days. The gauze was changed daily. The tube was removed the tenth day. Tetanus antitoxin was given in large doses intraspinally, intravenously, and intramuscularly. Avertin, 6 to 8 Gm., was administered, divided into a morning and afternoon enema. The patient was nourished by vein and nasogastric tube.

Three days after admission, the convulsions became less frequent and were gone by the eighteenth day, on which the mouth could be opened slightly. On the twenty-fifth day, the patient could take nourishment by mouth.

R. J. WEISSMAN.

Special Article

THEOPHILUS PARVIN

An Important Influence in American Obstetrics and a Pioneer in Clinical Teaching

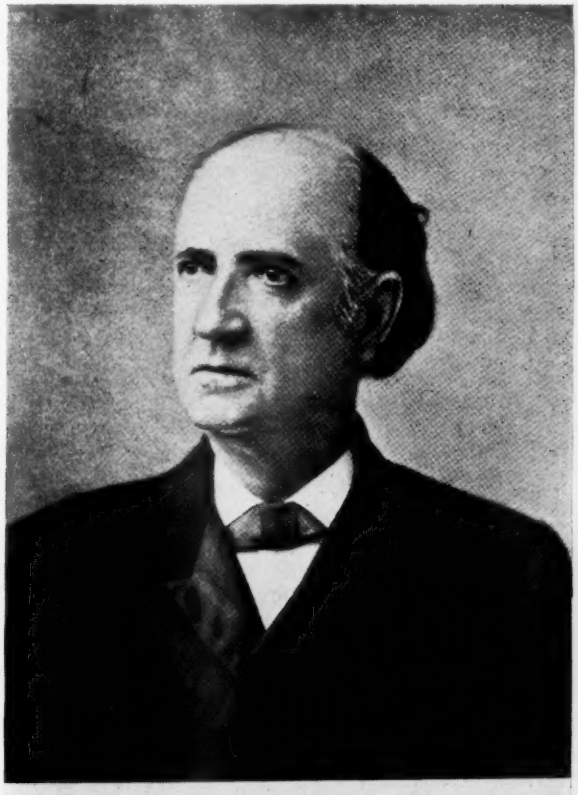
Herbert Thoms, M.D., New Haven, Conn.

"NO MAN in either hemisphere has been more widely recognized for his contributions to the subject of Obstetrics," says G. C. Mosher of Theophilus Parvin, whom he styles The Apostle of Casuistry in Medicine. Whether or not this statement may be debated, this author's appraisal of this important American obstetrician is stimulating and revelatory. Theophilus Parvin will be remembered in historical annals for at least two significant achievements, his authorship of an obstetric text which is remarkable for its sound doctrine and literary style, and his pioneer role in establishing in America the hospital instruction in obstetrics for medical students.

A survey of Parvin's *Science and Art of Obstetrics,* published in 1886, impresses one with the truth of a biographer who said that it "teemed with the characteristics of the man." In appraising his work, however, we are at once reminded that the author lived in a period of this country's history which in its writings and on the lecture platform was marked by a rhetorical splendor which, in spite of its extravagance, reflected a good deal of the spirit of that age. We are apt to smile at the ciceronian efforts of some of the medical orators of that day, but there is little doubt that could we have sat at the feet of a Meigs or a Parvin we would have attended with the same enthusiasm and acclaim as did our fathers. Such men as these did more than excel in the art of oratory, for they have left evidence that they were also excellent teachers of clinical medicine and possessed a knowledge of pedagogics which their medical descendants have too greatly ignored.

W. H. Parish says of Parvin that his acquaintance with the literature of obstetrics was probably unsurpassed by any of his contemporaries, and this is not difficult to believe for his writings reflect an erudition truly remarkable. His familiarity with the writings of the ancients as well as with The Bible and The Talmud are greatly in evidence. Although a profound literary stylist, his works show much original thinking which manifests itself in sound and at times prophetic doctrine. An understanding of this may be gained from noting some observations in his obstetric text. In discussing the bony pelvis he states that "in some instances the points of difference are so slight that it is very difficult to decide whether a pelvis is male or female," a point long recognized by anthropologists and forgotten by many medical writers since his time. His care of the prenatal patient sounds a familiar modern note, for he recommends that, "The obstetrician should visit the preg-

nant woman from time to time, especially during the latter weeks of pregnancy, so that he may know her condition is favorable for her approaching trial. Once a week during her last two or three months of gestation, the urine should be examined with reference to possible albuminuria." Regarding anesthesia he quotes a European authority speaking of nitrous oxide oxygen, "it can be inhaled for hours without any bad results. In most cases its results were entirely satisfactory, but in some it produced temporary violent excitement." Parvin also recommends elective cesarean section, recognizes the usefulness of episiotomy, and



Theophilus Parvin

was far advanced for his day in his knowledge of the etiology and treatment of puerperal sepsis. In 1885 he actually experimented with the local application of a solution of 4 per cent cocaine to effect local anesthesia. The results were negative, however.

An example of Parvin's oratorical style is seen in his tribute to O. W. Holmes in his address at the International Medical Congress in 1876. He writes, "Empedocles combined in one, poet, priest, politician and physician; and history records that he rescued a city from desolation by blocking up a mountain gorge through which pestilential winds were sweeping. In like manner an American whom the world knows as poet,

essayist and philosopher, that arrayed in these glories, crowned with these honors, we almost forget that he is a physician and medical teacher, once by his bold decisive utterances, his startling array of facts, his invincible logic, greatly contributed to destroy a pernicious doctrine taught by some of our leading obstetric authors—a doctrine which was more certainly laden with death than the foul wind that was destroying the citizens of Agrigentum."

Among the writings of Parvin we should not overlook his *Lectures on Obstetric Nursing*, a small work of less than 100 pages and a medical classic. This work was originally two lectures which the author gave for nurses at the Philadelphia Hospital. Here again his views regarding asepsis and antisepsis and the control of puerperal fever show real vision for his time. He emphasizes the value of the nurse making prenatal visits to her patient and recognizing untoward signs and symptoms so that they may be reported. Indeed, so much of Parvin's thought has not been outmoded by present-day opinion that the republication of this little volume would be a useful enterprise.

The pioneer role of Theophilus Parvin in the teaching of clinical obstetrics in hospital practice is shown in his address before the American Academy of Medicine in New York in 1888. This is entitled "The Necessity for Practical Obstetrics in the Course of Instruction Given by Medical Schools." Here he states that he was made conscious of the great deficiency in the American plan of obstetric instruction while on a visit to Munich where he had observed the teaching of Winckel. He presents a detailed account of Winckel's method as observed by J. Clifton Edgar, who for five months was resident obstetrician at the Munich Frauenklinik. This account is important aside from its historic interest because of its application to the present-day problems of clinical teaching. Speaking of the actual practice of each student before graduation in Munich he writes:

> "In the first place, he is required to attend the Obstetrical Clinic two semesters (winter five months, summer four months). Supposing he is called down in this clinic every two weeks, in that case he would touch (thoroughly examine externally and internally) eighteen gravid or parturient women. This is a low estimate. At the very lowest estimate, then, the student must have examined eighteen gravid or parturient women and conducted four labor cases, and taken the operation course on the phantom for one semester. The majority of students who come up for State examination in Munich have also taken a private 'touch course.'
>
> "In one of these courses, extending over five months (one semester), each student, at the very lowest estimate, examines both externally and internally, and each case several times, not less than forty cases. This course is not prescribed by law. My friends among the recent graduates in Munich informed me that the majority of students take one or more of these 'touch courses.'
>
> "Many students also see and conduct more labor cases than are prescribed by the State. Thus, for example, a German friend, recently graduated, informed me that while a student he conducted ten cases of labor in the clinic, and he did not seem to think he was getting more than his share.
>
> "Many students serve during vacation in what is known as the Polyclinic. Here they are called to abnormal cases of labor that may occur in the city, and in this way they see many additional cases."

In commenting upon these statements Parvin points out that the vast majority of American medical students are graduated without ever having witnessed, still less had charge of, a case of labor. The remedy, he states, lies in the practical teaching of obstetrics being directly associated with its scientific instruction . . . in other words there should

be a maternity belonging to every medical school in which practical obstetrics is taught. It was through the effort of Theophilus Parvin that the trustees of Jefferson Medical College in 1886 authorized the establishment of the first maternity department in any American hospital and assigned three rooms for the purpose. Work was begun in February, 1887, and at the time of his writing thirty-four women had been successfully delivered, the ward classes having been instructed by Parvin's assistant, Dr. William E. Ashton. In November, 1887, because of lack of room in the hospital, the out-patient department was established where clinical instruction was also carried out. In his peroration he states, "May the time soon come when every medical school which does not take this step, and make this necessary reform, shall perish under the common and condign, popular and professional damnation." At a later date, as President of The American Gynecological Society and speaking on the same subject, he sounded this prophetic note, "The true ideal can only be realized in a large hospital devoted to obstetrics and diseases of women, students being taught in a small number at a time."

Interesting to us in this latter address are Parvin's comments on the use of the word Gynecology, because much confusion still exists as to its correct usage.

> "Let me, by an appeal to etymology," he states, "rescue gynecology from its narrow use, . . . gynecology should be regarded as a synonym for obstetrics rather than for diseases of women, and the gynecologist is primarily an obstetrician. . . . The word gynecology, both etymologically and in its essential signification, relates to reproduction in the human female, and secondarily to the diseases and disorders which interfere or prevent this function, or those which are consequent upon its exercise."

It is also important to remember Parvin's significant part in the union of obstetrics and gynecology as branches of medical instruction. In this he was ably supported by the opinions of Winckel to whom he had written for advice on the subject. Space does not permit an account of the conclusions of this eminent European teacher, but his views on the subject cannot be overlooked by those who, even today, do not favor such amalgamation in hospital practice or for purposes of clinical instruction.

Mosher refers to Parvin as "The Apostle of Casuistry," and by this he interprets "Casuistry," as did Parvin, in its original classical meaning, the application of ethical principles to questions of conscience and judgment. It is probable that no modern medical writer so concerned himself with this aspect of medicine as did Theophilus Parvin. Throughout his writings we are impressed with his sound logic concerning the difficult problems that are so often associated with the forming of medical opinion. An example of his manner is seen in his discussion of the diagnosis of pregnancy.

> "Ambition to give a prompt decision," he writes, "or pride in opposing that of another, may lead to error. Rapidity is very far from proving correctness of diagnosis; here, as Lord Bacon has said of another matter, our intellects need not wings but weights of lead to moderate their course. The man of greatest knowledge least exalts his attainments, and is the most cautious and deliberate in judgment, and has respect for the opinions of others. Sloth may hinder or prevent our thorough investigation. We may be satisfied with a few facts instead of seeking all that are available."

Such excerpts from the writings of Theophilus Parvin tell us something of the man, but only in his *Science and Art of Obstetrics* do we realize the lofty spirit and broad clinical knowledge that he brought to

his subject. I know of no other text of his time which is so fraught with lessons for today or which can be more useful to the student who wishes to attain a knowledge of the fundamental background of modern obstetrics.

The facts of Parvin's life are readily available in the usual sources of biography, but it may be useful to repeat some of them here.

Theophilus Parvin was born in Buenos Aires on Jan. 9, 1829. His father, of the same name, was a missionary to the Argentine Republic, having prepared for the ministry at the University of Pennsylvania and the Princeton Theological Seminary. His mother was the daughter of Caesar Augustus Rodney, one time Attorney-General of the United States and later Minister to the Argentine Republic. Parvin's mother died when he was an infant and his father brought him to this country. At the age of seven the father died and the boy went to live with a guardian, the Rev. Dr. Steel of Abington, Pa. When twelve years of age Parvin entered the preparatory department of Lafayette College and later entered the University of Indiana from which he received his bachelor's degree in 1847. For the next three years he taught at the Lawrenceville High School at the same time studying Hebrew and Greek at the nearby Princeton Theological Seminary. In 1850 he received his master's degree from the University of Indiana and in 1852 his medical degree from the University of Pennsylvania. He became an interne at the Wills Eye Hospital in Philadelphia and later a ship surgeon on a packet line sailing between Philadelphia and Liverpool. He then settled in Indianapolis where he practiced until the close of the war. In 1864 he was elected to fill the Chair of Materia Medica in the Ohio Medical College, and in 1869 he resigned to accept that of Obstetrics and Diseases of Women at the University of Louisville. In 1876 he accepted a similar chair in the College of Physicians and Surgeons of Indianapolis and two years later became Professor of Obstetrics, et cetera, at the Medical College of Indiana. In 1882 he was recalled to the chair previously held by him in the University of Louisville. The next year he was called to the Chair of Obstetrics and Diseases of Women and Children at Jefferson Medical College, Philadelphia.

During his professional life many honors came to Theophilus Parvin, among which may be numbered the Presidency of The American Medical Association, of The American Gynecological Society, of The American Academy of Medicine and The Philadelphia Obstetrical Society. In addition to the writings mentioned above, he translated *Winckel's Diseases of Women* and wrote for *Ashurst's Encyclopedia of Surgery, The American Textbook of Obstetrics* and *The American Textbook of Applied Therapeutics.* Other of his important accomplishments could expand this all too brief outline into greater proportion, for Parvin's life was one of intense activity and fulfillment. In his obituary, which appeared shortly after his death in the *Journal of the American Medical Association,* we find this note which tells its own story of affliction and personal courage:

"About eight years ago when examining a patient he inoculated his index finger with specific poison, and recognizing the nature of the affection he called the attention of the class to it on several occasions as a warning to them to be always on their guard. His health subsequently became impaired and he suffered with a severe form of chronic laryngitis which compelled him for a time to suspend his lectures; of recent years, however, this affliction had been overcome so that he not only resumed his course of lectures, but was able to accept complimentary invitations to address medical societies."

Like his distinguished contemporaries, Hodge and Meigs, Parvin's life as a physician and teacher was one of great fulfillment. To the field of obstetric science he brought a maturity of mind and keenness of vision which reflected itself in his writings and teachings. It was fortunate that the advent of scientific obstetrics in America had among its followers so great a champion as Theophilus Parvin.

"'Tis man's worst deed
To let the things that have been, run to waste
And in the unmeaning Present, sink the Past."

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Lissimore and Currie: Studies in Vaginal Fluid, J. Obst. & Gynaec. Brit. Emp. **46:** 673, 1939.

A series of 105 cases of vaginal discharge was examined. The majority of patients (66.9 per cent) were the hosts of *Trichomonas vaginalis.* This organism in the opinion of the authors is not pyogenic but is associated with a lowering of the normally high acidity of the vaginal contents, and thus with removal of one of the most powerful barriers to infection by pyogenic invaders, of which the *Staphylococcus pyogenes aureus* is by far the commonest in their series. This accounts for the frequent association of the flagellate with pus, secondary infection being more usually present. There are two possible explanations of this association of the flagellate with decreased acidity:

A. The trichomonas is antagonistic to the bacillus of Döderlein. It also impedes the normal desquamation of vaginal epithelium. Thus both factors, closely associated with normal vaginal acidity, are reduced or absent.

B. The acidity of the vagina suffers great antecedent reduction by at least two natural factors, namely (1) the presence of menstrual lochia during periods, and (2) the deposition of semen during intercourse. The trichomonas, finding once again a medium of a pH agreeable to its existence, readily reestablishes itself. It is thus not necessary to postulate direct infection from the male during intercourse. Either of these two factors would explain the reappearance of trichomonas after apparent cure.

In the 33.1 per cent of cases in which trichomonas is absent, pyogenic infection explains the qualitative abnormalities of the vaginal fluid, and, as in the trichomonas positive cases, the *Staphylococcus pyogenes aureus* appears to be the commonest invader.

J. P. Greenhill.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

MATERNAL MORTALITY, 1939

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THE lowest maternal mortality rate ever recorded in the United States, 40 per 10,000 live births, has been reported by the Bureau of the Census for the year 1939. The maternal mortality rate for all causes decreased 9 per cent during 1939 (from 44 per 10,000 in 1938 to 40 per 10,000 in 1939). The maternal mortality rate for 1939 was 32 per cent lower than that for 1934, before the initiation of a nation-wide program of health services for mothers and children under the Social Security Act. This is a much larger gain than was attained in the five years before the Act was passed. From 1930 to 1934 the maternal mortality rate for the United States dropped only 12 per cent. The death rate for all causes for persons of all ages has decreased only 5 per cent since 1934.

A total of 9,151 women died in 1939 from conditions of pregnancy and childbirth; 6,995 of these women were white, 2,083 were negro, and 73 were of other races. The maternal mortality rate for negro women (77) was more than double the rate for white women (35). The mortality rates for both white and negro women have decreased in recent years, but the decrease has been much greater among the white than among the negro.

Maternal mortality rates varied from a low of 22 in Idaho to a high of 65 in Florida (see Table I).

The majority (5,613, or 61 per cent) of the 9,151 women whose deaths were classified as maternal in 1939 died during or after childbirth; 24 per cent (2,160) died following abortions or ectopic gestation, and 15 per cent (1,378) died undelivered (see Table II). Childbirth in the 1938 revision of the International List is defined as the termination of a uterine pregnancy after seven lunar months (twenty-eight weeks or more) of gestation. Abortion is defined as the termination of a uterine pregnancy before seven lunar months (twenty-eight weeks) of gestation.

The pregnancies of 1,786 of the 2,160 women who died after abortion or ectopic gestation were uterine pregnancies, and 374 were extrauterine. The abortions of 220 women were stated to have been self-induced and those of 157 to have been criminal.

More than 70 per cent (990) of the 1,378 women who died undelivered died from toxemias of pregnancy. Only 61 died from hemorrhage. For almost one-fourth (327) of these deaths, the physician gave no real information as to the cause, but merely entered the fact of pregnancy or that the mother died before the baby was born.

Infection was responsible, in all, for 42 per cent (3,834) of the 9,151 deaths. More than 60 per cent (2,353) of the women who died from this cause died during or after childbirth, but 1,393 died after abortion and 88 from ectopic gestation.

Toxemias of pregnancy were responsible, in all, for 24 per cent (2,232) of the 9,151 deaths. Slightly more than one-half (1,149) of these 2,232 women died during or after childbirth; 990 died before delivery and 93 after abortion.

Hemorrhage, trauma, and shock were responsible, in all, for 20 per cent (1,808) of the 9,151 deaths. Most (1,617) of these 1,808 deaths occurred during or after childbirth; 130 were due to hemorrhage following abortion, and 61 to hemorrhage of pregnancy.

TABLE I. MATERNAL MORTALITY, BY STATES, 1939

STATE (NUMBER OF DEATHS IN 1939)	MATERNAL MORTALITY RATE*	STATE (NUMBER OF DEATHS IN 1939)	MATERNAL MORTALITY RATE*
United States (9,151)	40	Maryland (105)	37
Idaho (24)	22	Kansas (108)	37
North Dakota (32)	24	Pennsylvania (613)	38
Oregon (40)	24	Maine (59)	39
Connecticut (60)	26	Ohio (424)	39
Wisconsin (151)	28	Oklahoma (176)	40
South Dakota (34)	29	Nevada (8)	41
Minnesota (148)	29	Delaware (18)	41
Iowa (131)	30	Missouri (243)	41
Utah (40)	31	Kentucky (262)	43
Michigan (289)	31	Arizona (48)	44
California (321)	31	North Carolina (374)	47
Illinois (370)	31	Texas (590)	49
Montana (35)	32	New Mexico (71)	50
New Jersey (182)	32	Virginia (268)	51
New York (603)	32	District of Columbia (73)	52
West Virginia (136)	33	Colorado (111)	54
New Hampshire (27)	34	Tennessee (297)	56
Rhode Island (35)	34	Georgia (362)	56
Wyoming (17)	35	Arkansas (202)	57
Nebraska (78)	35	South Carolina (253)	59
Massachusetts (224)	35	Mississippi (307)	59
Vermont (23)	36	Alabama (361)	59
Washington (95)	36	Louisiana (302)	62
Indiana (210)	36	Florida (211)	65

*Maternal deaths per 10,000 live births.
Based on data from the Bureau of the Census.

TABLE II. MATERNAL DEATHS FROM EACH CAUSE AND TIME OF DEATH WITH RESPECT TO DELIVERY, UNITED STATES, 1939*

CAUSE OF DEATH	TOTAL		ABORTION AND ECTOPIC GESTATION NO.	DURING PREGNANCY NO.	DURING OR AFTER CHILDBIRTH NO.
	NUMBER	PER CENT DISTRIBUTION			
All causes	9,151	100	2,160	1,378	5,613
Infection	3,834	42	1,481	--	2,353
Toxemias of pregnancy	2,232	24	93	990	1,149
Hemorrhage, trauma, and shock	1,808	20	130	61	1,617
Other specified causes	471	5	456	--	15
Causes not stated	806	9	--	327	479

*Based on data from the Bureau of the Census.

Physicians failed to give satisfactory information as to cause for 9 per cent (806) of the 9,151 maternal deaths. These deaths include those for which the physician stated the cause in such general terms as pregnancy, multiple pregnancy, and dead fetus in utero, or indicated little more than that a child had been born to the mother and that the birth was the most important factor in the death.

There were 2,265,588 live births registered in 1939. About one-half (1,138,185) of these births occurred in rural areas, the other half (1,127,403) in urban areas, that is, in cities of 10,000 or more population. Slightly over half (51 per cent)

of all live births in the United States occurred in hospitals, but 81 per cent of all live births in cities occurred in hospitals, as compared with 22 per cent of live births in rural areas. Of all white infants, 55 per cent were born in hospitals, as compared with 23 per cent of the negro infants.

The proportion of births in hospitals has increased considerably during the period of record. In 1935, 37 per cent of the live births occurred in hospitals, as compared with 51 per cent in 1939.

SUMMARY

The reduction in the maternal mortality rate attained in 1939 and in each of the five years of Federal and State cooperation under the Social Security Act is well marked. The lives of 11,000 mothers have been saved during the period 1935 to 1939 that would have been lost had the maternal mortality rate of 1934 prevailed through these years; and the lives of 800 mothers were saved in 1939 that would have been lost had the mortality rate been as high in that year as in 1938. If the maternal mortality rate of 24 already achieved by 3 states had been applicable to the entire United States in 1939, there would have been only 5,437 deaths instead of 9,151.

A concentrated effort should be made to extend and improve medical and hospital services in the states with the highest mortality. A maternal mortality rate of less than 20 per 10,000 live births now seems possible of attainment. This rate will, however, be attained for the country as a whole only when every maternity patient seeks and can obtain competent medical care throughout the maternity cycle and, when needed, care in a hospital with an approved maternity service.

Fleck, Stephen, Snedeker, Elizabeth F., and Rock, John: The Contraceptive Safe Period, New England J. Med. **223**: 1005, 1940.

A detailed analysis is presented of observations and results as recorded by the Rhythm Clinic of the Free Hospital for Women in Brookline, Mass., covering a period of not quite four years.

A few important data only can be quoted from this elaborate report.

"The fertile period extends from and including nineteenth day before the *earliest* likely menstruation up to and including the ninth day before the *latest* likely menstruation. In each case the apprehended dates of menstruation are derived from the patient's written record of previous catamenial dates."

For about 6 per cent of the women applying for advice, the method was inapplicable; at least 14 per cent of those who could use it became dissatisfied; approximately 6 per cent were incapable of observing the rules; and about 3 per cent of the patients suggested true failure of the method. The figures indicate that though the corrected failure rate among 207 patients is only 3 per cent, the method is inappropriate for about one-third of women.

Their final conclusion is that the safe-period method constitutes a workable form of contraception for a selected group of women. On the other hand, it is doubtful whether the method is reliable enough for individual cases in which contraception is an essential safeguard of the patient's health.

HUGO EHRENFEST.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

HOW CAN THE OBSTETRICIAN AID IN REDUCING THE MORTALITY OF PREMATURELY BORN INFANTS?*

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DURING the year 1939, 99,700 infants of known weight were born alive in the city of New York. Of these, 7,291, or 7.3 per cent, weighed under 2,500 Gm. Since this weight level is considered a good index of prematurity, it may be stated that the incidence of prematurely born living infants in New York during that year was approximately 7.3 per cent.

Thirteen hundred and forty-one, or 18.4 per cent, of these 7,291 infants who weighed under 2,500 Gm. died during the first month of life, while only 948, or 1.2 per cent, of those above 2,500 Gm. failed to survive the same period (Table I). The

TABLE I. INFANT DEATHS UNDER ONE MONTH (NEW YORK CITY, 1939)

	TOTAL BIRTHS	TOTAL DEATHS	PER CENT
Infants of known weight	99,700	2,289	2.3
Infants under 2,500 Gm.	7,291	1,341	18.4
Infants over 2,500 Gm.	92,409	948	1.2

hazard for the premature, accordingly, was over fifteen times as great as was that for the child born at term. Although the prematurely born infants made up only 7.3 per cent of the total 99,700 live births of known weight, the prematures who died within thirty days constituted almost 60 per cent of all of the deaths under one month.

From these figures, it is evident that any appreciable lowering of the death rate in the first month of life can be accomplished only by lowering the 7.3 per cent incidence of premature deliveries or by reducing the 18.4 per cent mortality of this group.

The first of these considerations, namely, the prevention of premature interruption of pregnancy, falls entirely within the realm of obstetrics. The lowering of the 18.4 per cent mortality for the first month is a matter for joint consideration by the obstetrician and the pediatrician. The fact that the obstetrician turns a living premature infant over to the pediatrician does not absolve him from all blame, should the infant fail to survive. On the other hand, pediatricians often are reluctant to assume even their share of the responsibility. A review of the reports of various pediatric services which include the care of the newborn infant shows a growing tendency to list premature deaths into three groups: Those who fail to survive twenty-four hours; those who die within forty-eight hours; and those who are lost within one month. Behind this tendency is the intent to shift the responsibility for the first two groups back upon the obstetrician. In some instances, the pediatricians have even gone so far as to tell the obstetrician how he should deliver these individuals. When such a state of affairs is reached, it is time for us

*Read at a meeting of the Michigan Society of Obstetricians and Gynecologists at Detroit, Michigan, December 3, 1940.

obstetricians to review the situation seriously and correct our own shortcomings before those who are less competent attempt to correct them for us.

Premature deaths in New York City have been tabulated for the first twenty-four hours as well as for the first month of life (Table II). These figures show

TABLE II. MORTALITY UNDER ONE MONTH AND UNDER ONE DAY BY WEIGHT GROUPS NEW YORK CITY, 1939

WEIGHT GM.	TOTAL BIRTHS UNDER 2,500 GM.	DEATHS UNDER ONE MONTH		DEATHS UNDER ONE DAY	
		NO.	MORTALITY %	NO.	MORTALITY %
Under 1,000	370	344	93.0	289	80.0
1,000 to 1,500	582	376	64.0	243	42.0
1,500 to 2,000	1,326	318	24.0	167	12.6
2,000 to 2,500	5,013	303	6.0	144	2.8
Total	7,291	1,341	18.4	851	11.6

the startling fact that 851, or over 63 per cent, of the 1,341 deaths under one month occurred on the first day. If the obstetrician believes that his responsibility ends with the birth of the child; and if the pediatrician refuses to accept responsibility for all infants who do not live over twenty-four hours, are we to conclude that these 851 infants, who comprised 63 per cent of the deaths under one month, were abandoned? Of course, they were not abandoned as individuals. The physician instinct in both the obstetrician and pediatrician made them give to each of these prematurely born infants the best of their efforts. Nevertheless, these 851 infants as a group were neglected in the sense that constructive thought has not been directed toward their welfare by the two specialties which should be jointly responsible for that welfare.

Of the 370 infants weighing under 1,000 Gm., 80 per cent died on the first day and 93 per cent within one month (Table II). Almost half of those between 1,000 and 1,500 Gm. failed to live twenty-four hours, and about two-thirds of this group survived less than one month. From these figures, it seems reasonable to conclude that the best way to prevent mortality in the groups of infants weighing under 1,500 Gm. is to prevent the conception of such infants or to delay their birth until they are large enough to withstand the hardships of extrauterine life. This conclusion is further substantiated by the fact that the largest percentage of prematurely born infants who have intracranial hemorrhage, as well as the largest percentage of surviving prematures who are mentally defective, are to be found in the infants who weigh under 1,500 Gm. at birth.[1]

Although some of the arguments offered in favor of contraception and sterilization are open to controversy, women who have progressive hypertensive disease, nephritis, severe diabetes, and the graver types of anemia should be sterilized or should practice contraception. In the milder anemias and other diseases due to nutritional deficiencies, as well as in syphilis and active tuberculosis, pregnancy should be avoided until the condition is cured.

Fig. 1 graphically shows the large proportion of infants who died on the first day and strikingly illustrates the marked reduction in mortality which accompanied each 500 Gm. addition in weight. From this chart, we may again conclude that the best way to lower the death rate of infants under 1,500 Gm. in weight is to prevent conception or to prolong their intrauterine life. In fact, the great reduction shown for each shift to the right directs our attention to the value of prolonging the pregnancy in each of the weight groups. In the so-called causeless cases of premature birth which, incidentally, are the most frequent of all premature deliveries, this can be accomplished, to a large extent, by more careful supervision of the hygiene of pregnancy.

PRENATAL CARE

Among the various items which are included in all good prenatal care routines, certain measures are of particular importance. These include early examination

by the physician, routine laboratory and physical examinations throughout pregnancy, careful instructions concerning diet, coitus, rest and exercise, and emphasis on the need for immediately informing the physician whenever any untoward symptoms occur.

Incorrect conceptions regarding daily food requirements are so prevalent that careful instructions concerning the proper balancing of the diet during pregnancy are imperative. These instructions should be specific. They likewise should consider the likes and dislikes of the individual patient. In clinic practice, where the financial status of the patient makes it difficult for her to obtain the more costly foods, she should be shown how proper nourishment can be secured within her means. This may require instruction not only in the purchase of foods but in the

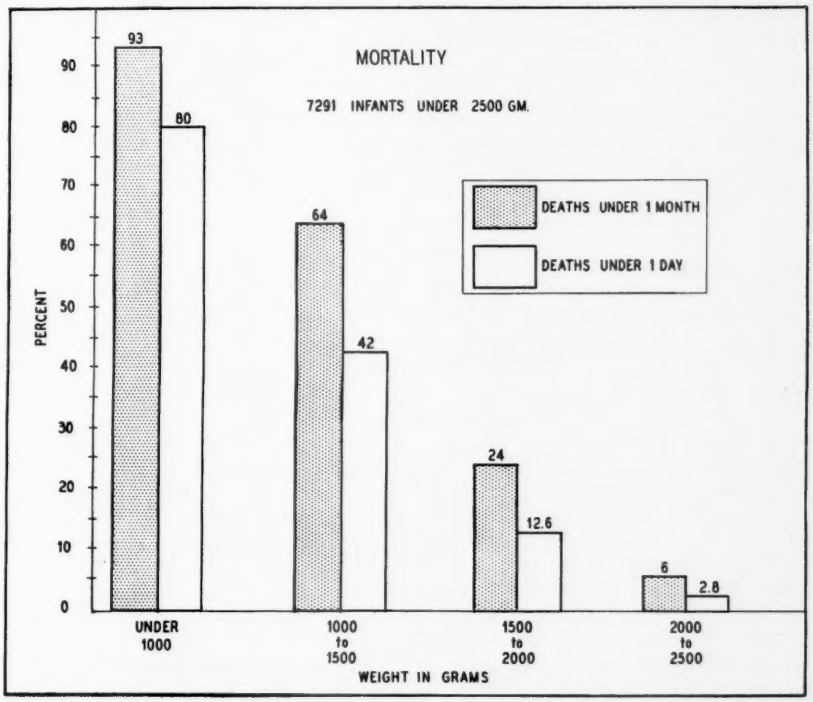

Fig. 1.—Deaths of infants under 2,500 Gm. during the year 1939 in New York City. The percentages are plotted along the perpendicular and the various weight groups along the base line. The stippled figure represents the mortality during the first month of life while the open one shows the percentage of deaths on the first day. For each addition of 500 Gm. in weight, the percentage of deaths on the first day, as well as during the first month, is greatly reduced.

make-up of menus and in the actual preparation of the less costly articles. In our Clinic, we have devised balanced diets for each month of the year at an average cost of slightly over thirty cents per day. We also are preparing a set of instructions which includes the methods of cooking which will make these inexpensive foods more palatable.

Rest and Exercise.—Proper advice concerning rest and exercise should aid in reducing the incidence and mortality of prematurity. Adequate sleep at night and some rest in the middle of the day are essential for all pregnant women. This is particularly important during the last half of pregnancy and is imperative in those women who have any of the conditions which predispose to premature labor. Whenever spontaneous interruption of pregnancy seems imminent, complete and prolonged rest in bed is indicated and large doses of progesterone should be given

to lessen the irritability of the uterus. Violent exercise should be prohibited. This prohibition includes tennis, horseback riding, and the more strenuous sports. Moving of furniture and other exertions which necessarily accompany house cleaning and change of domicile are too strenuous for the woman who is pregnant and are quite certain to cause disaster in those who are predisposed to the interruption of gestation. The same may be said of long journeys by auto, railroad, or steamship during which the constant vibration may cause the onset of labor.

Sexual Relations.—Because coitus may bring on labor, abstinence from sexual relations in the last trimester is advisable. This precautionary measure is especially indicated in those women who have had a blood-stained vaginal discharge at any time during pregnancy as well as in those who have shown evidence of the predisposing causes of prematurity.

Danger Symptoms.—Finally, it should be the aim of prenatal care to bring the patient into touch with her physician whenever headache, edema, rapid gain in weight, or visual disturbances appear as evidences of toxemia, or whenever abdominal pain and vaginal bleeding indicate the imminence of premature labor, in order that immediate steps may be taken to prolong the pregnancy. These should include rest in bed, the administration of large doses of progesterone, and the treatment of the underlying cause of the uterine irritability. Some of the predisposing factors are sufficiently important to warrant separate consideration.

TOXEMIA

Toxemia often is responsible for the premature interruption of pregnancy, and, in some reports, it heads the list of etiologic factors. Since careful supervision of the hygiene of pregnancy will usually prevent its occurrence, adequate prenatal care offers the best means of diminishing premature births and premature mortality from this cause.

In the presence of an uncontrollable and rapid increase in blood pressure, albuminuria and edema, continuance of the pregnancy subjects the mother to the danger of eclampsia. At the same time, there is considerable risk that the child may perish in utero. The interests of the mother and child, therefore, call for a rapid emptying of the uterus.* Cesarean section, accordingly, is given preference over the ordinary methods of inducing labor. When the operation is done under local anesthesia and without preliminary sedation, an excellent maternal and fetal result is the rule. The use of sedatives prior to operation, on the other hand, increases the risk to the fetus and general anesthesia adds greatly to the hazards of mother and child.

Intermediate between the cases in which prophylactic care eliminates all cause for anxiety and those rare ones in which only radical interference prevents a catastrophe, are to be found various perplexing gradations of toxemia. If the condition cannot be relieved but does not progress, pregnancy should not be interrupted until the fetus has reached a size compatible with extrauterine existence, even though prolongation of the toxemia may lead to residual vascular damage in the mother. In all such cases, as well as in those which slowly progress in spite of treatment, the fetus in utero, as well as the mother, is entitled to the benefit of competent consultation. This consultation, together with roentgenologic estimation of the size of the fetus, should eliminate the majority of premature labors which are induced before the weight of the fetus reaches 1,500 Gm.

CARDIAC DISEASE

Cardiac disease may also be responsible for spontaneous or artificial interruption of pregnancy before term is reached. Such interruptions usually occur during or soon after congestive failure in women who have severe heart lesions. Most of these patients begin their gestations with a cardiac reserve which is unequal to the strain of pregnancy. In the majority of them, a careful history and physical examination before conception is permitted would reveal the fact that the cardiac condition is too grave to warrant the risk of pregnancy. Proper preconceptional advice,

therefore, will eliminate the possibility of premature delivery and premature mortality in most instances of this character. However, many of these unfortunate women, who are under the care of their physician, either receive no advice concerning the risk of pregnancy or they disregard such advice. As a result, the seriousness of this complication is not realized until they present themselves for prenatal examination.

Congestive failure resulting from the extra load of pregnancy is not uncommon in these cases and, because of it, the pregnancy may be interrupted prematurely. In Hamilton's series of 514 cardiac patients, 53 were thus terminated.[2] While the infant mortality was slightly less than 4 per cent after the thirty-fifth week, over 50 per cent of the viable infants delivered prior to the thirty-sixth week were lost. Thus it may be stated that the premature infant is particularly susceptible to the effect of congestive failure in the mother, even though the more mature fetus is relatively unaffected thereby.

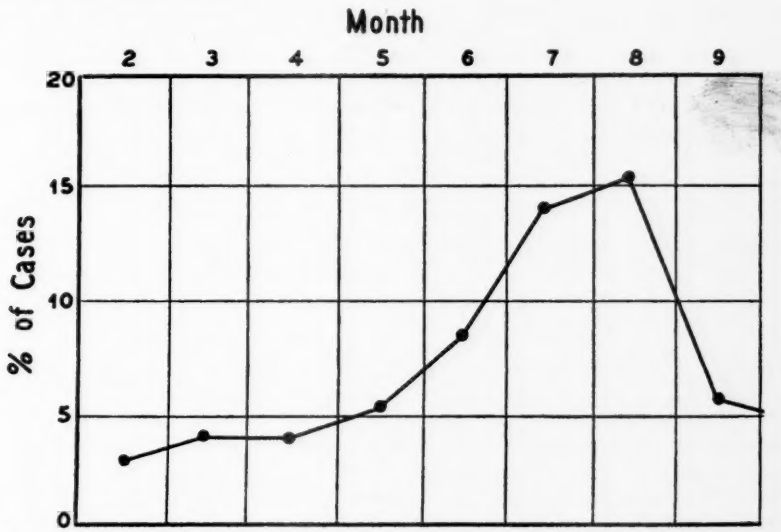

Fig. 2.—Incidence of cardiac failures in the various months of pregnancy (Carr and Hamilton). Note the precipitate fall in the number of failures after the eighth month.

Because the risk to the fetus in these cardiac cases decreases rapidly with each added month of intrauterine life, it is essential that spontaneous interruption of gestation be prevented and artificial termination be postponed as long as the best interests of the mother will permit. In this connection, it may be well to note the observations of Carr and Hamilton concerning the period of gestation in which congestive failure is most likely to occur (Fig. 2). While, according to them, congestive failure may occur at any month, the incidence of its occurrence is rather low up to the sixth month, after which it rises rapidly to reach a peak in the eighth month. Soon thereafter the tendency toward a break in compensation rapidly diminishes. These observations concerning the decrease in both maternal and fetal risk after the eighth month make imperative obstetric and cardiologic consultation in order that both mother and child may have the benefit of the optimum time for delivery.

Because the combination of prematurity and congestive failure is decidedly unfavorable for the child and because delivery or operative interference during a break in compensation is most hazardous for the mother, a pregnancy should not be terminated artificially in the course of congestive failure. By waiting until the patient has recovered from the break in compensation or until no further improvement is possible, both the mother and child will have a better chance for survival.

Under proper medical management, the improvement which takes place after the eighth month when the blood volume begins to fall, is often so great that spontaneous delivery at term may be awaited and all thoughts of terminating the pregnancy dismissed.

Patients with well-compensated lesions, without a history of previous failure, seldom have difficulty and, in them, the risk to the child is approximately the same as for noncardiac cases, provided they are properly supervised. Because cardiac lesions, even when well-compensated, are treacherous complications, joint care by the cardiologist and obstetrician is most desirable.

SYPHILIS

Although most investigators attach less importance to syphilis as a cause of prematurity than was the custom in former years, maternal syphilis still occupies a prominent place among the etiologic agents. Since it occurs four and one-half times more commonly among the colored than among the white mothers,[3] the control of syphilis is of particular importance in the prevention of prematurity in our colored population.

Because the usual manifestations are mild or masked in many women, and because the disease tends to be latent during pregnancy, the Wassermann reaction should be determined as a routine measure early in every pregnancy. As soon as the diagnosis is made, treatment with arsphenamine and bismuth should be commenced. Early and thorough use of these drugs will assure the birth of a living and healthy child in at least 90 per cent of the cases. The recognition and treatment of syphilis during pregnancy, accordingly, is one of the most fruitful fields for the prevention of premature birth and premature mortality.

PLACENTA PREVIA AND PREMATURE SEPARATION OF THE PLACENTA

While placenta previa and premature separation of the normally implanted placenta are rather rare in ordinary practice, these grave complications are relatively important causes of premature birth in obstetric hospitals. Although the occurrence of placenta previa is an unavoidable complication of pregnancy, premature separation of the placenta can be prevented in many instances by preventing the occurrence of toxemia. That part of prenatal care which has to do with the prophylaxis of toxemia, therefore, may also serve as a prophylaxis against some of the premature births which are caused by separation of the normally implanted placenta. Whether the underlying pathology can be prevented or not, much can be done to diminish the infant and maternal mortality which results from these major complications, by having the patient report to her physician whenever vaginal bleeding of any kind is observed.

The growing tendency to employ cesarean section in the treatment of placenta previa and ablatio placentae should increase the chances of obtaining a living infant capable of surviving. Reports from some clinics, however, do not justify such optimism. Although the mortality of the premature infants delivered by cesarean section for placenta previa at the Boston Lying-in Hospital was considerably lower than that obtained by other methods of treatment, fully 50 per cent of the infants thus delivered were lost.[4] It may be possible that the use of preoperative sedation and general anesthesia was responsible for some of these deaths. On the other hand, local anesthesia, without preliminary sedation, is used in our clinic and, in spite of this precaution, we have observed a higher mortality for prematures delivered by abdominal section in cases of placenta previa than for those similarly delivered in other complications. It may be possible that the loss of blood by the mother produces an anoxia of the fetal brain with residual damage, from which it is unable to recover. If this is true, more frequent and larger transfusions prior to operation should help the fetus as well as the mother.

While most good obstetricians subscribe to the dictum that there is no expectant treatment for placenta previa, the great improvement in and accessibility to obstetric hospitals may lead us to modify this dogmatic rule in the interests of the premature infant. Should this rule be so changed, those cases of placenta previa

which are then recognized before the fetus has a good chance of surviving, will be hospitalized and treated with large doses of progesterone to diminish the irritability of the uterus, in the hope that the bleeding may be arrested and the pregnancy prolonged until a child of more than 1,500 Gm. can be obtained.

MULTIPLE PREGNANCY

While the fetuses tend to be smaller in plural than in single pregnancies of the same duration, the additional risks of multiple pregnancy more than offset the added intrauterine life which premature twins enjoy over single pregnancy infants of similar weight. These risks include the greater tendency toward nutritional deficiencies, toxemia, cardiac failure, overdistention of the uterus, uterine atony, malpresentation and operative delivery. In multiple pregnancies, therefore, all of the recommendations concerning the hygiene of pregnancy are doubly important.

Because of the overdistention of the uterus, precaution should be taken to prevent the onset of premature labor. Once labor is established, its management should be as conservative as possible. The second twin should not be delivered by version and extraction just because the passages have been prepared by the delivery of the first twin. If the presentation of the second fetus is longitudinal, interference should be limited to rupture of the membranes and Nature should be permitted to complete the delivery. Only after a delay of at least one hour is version justifiable, since *version and extraction is a dangerous procedure when the fetus is premature.*

INTERRUPTION OF PREGNANCY

One of the most promising fields for improvement in our prematurity end-results is that which is concerned with the artificial termination of pregnancy. Regardless of the method employed to bring about the emptying of the uterus, the greatest improvement will come from a more careful consideration of the size of the fetus and the period of gestation. Thoms and others have observed a definite relationship between the length of the occipitofrontal diameter and the length and weight of the fetus.[4, 5] By the use of roentgen rays, the length of this diameter can be measured and from it the size of the fetus estimated. Whenever possible, therefore, the length and weight of the fetus should be determined by roentgenologic examination before pregnancy is interrupted. The unborn fetus also is entitled to the benefit of consultation with another experienced obstetrician in order that the pregnancy may be prolonged until the premature child's chance for survival is good. These two measures should accomplish much in the reduction of the mortality of prematurely born infants.

SEDATIVES

In the management of premature labors, the use of the various sedative drugs and anesthetics has caused considerable controversy. The work of Snyder and Rosenfeld shows definitely that all of the drugs ordinarily used for the purpose of producing analgesia, amnesia and anesthesia in the mother, have a depressing effect upon the fetal respiratory movements.[6] Their observation would seem to indicate that the immature brain of the premature infant should not be further handicapped by the depressing action of these drugs. On the other hand, Grier and Lussky, in a series of 453 premature infants, observed that the mortality for the infants whose mothers had been given these drugs was no higher than might be expected for their respective weight groups.[7] Since 410 of the 453 received sedation or anesthesia or both, the similarity in the end-results of the drug cases and the end-results of the entire series is to be expected. Comparison of their figures with those of New York City, likewise, shows a higher mortality among their drug and anesthesia cases for each weight group than is recorded for similar groups in New York. Although conclusions drawn from a comparison of this kind are not infallible, they seem to substantiate the deduction which might be drawn from the work of Snyder and Rosenfeld. Until further data are available, therefore, it is reasonable to conclude that sedative drugs and general anesthetics should not be given in the course of premature labor.

PRESSURE EFFECTS

Not only are the pressure effects of labor more injurious to the premature than to the full-term infant, but the frequency and extent of the damage done vary inversely with the duration of pregnancy. In other words, the smaller the fetus, the greater will be the risk of serious injury during delivery. Most of the danger is encountered in the second stage during which pressure on the uteroplacental circulation may cause oxygen deprivation varying from mild anoxia of the brain to complete asphyxia, or, pressure of the soft and malleable head against the resisting pelvic floor may produce brain injury and intracranial hemorrhage. On account of these dangers, the membranes should be preserved as long as possible and the second stage of labor should be terminated shortly after the head reaches the level of the ischial spines. The latter usually can be accomplished by doing an episiotomy under local anesthesia. Since this procedure removes most of the resistance at the outlet, it should be done in all cases. If the birth of the head does not follow soon after the episiotomy is done, extraction by low forceps is indicated. When the blades are carefully applied and only gentle traction is made, the low forceps operation protects the child's head from injury. As a result, low forceps after episiotomy gives the lowest mortality of all methods of delivery.

VITAMIN K

Because the brain of the premature fetus is poorly protected by the imperfectly developed intracranial supporting connective tissues and because the blood vessel walls cannot withstand as much pressure as those of the full-term infant, brain injury and intracranial hemorrhage are more common in premature than in full-term labors. If the child has a hypoprothrombinemia, the slightest injury to an intracranial vessel may cause serious bleeding. For this reason, vitamin K should be given to the mother several hours before premature termination of pregnancy is artificially attempted and every four hours during all premature labors.

CONSERVATION OF HEAT AND AUTOTRANSFUSION

Immediately after delivery and before the cord is tied, the newborn premature infant should be placed in a tub of warm sterile water to prevent the shock which might follow a sudden chilling of the body surface and to protect it against any unnecessary heat loss while waiting for the cord to stop pulsating. Often the cord is clamped and cut at once in order that the child may be immediately placed in an incubator. This practice is reprehensible since it deprives the immature infant of considerable blood which it otherwise might take up from the placental circulation. By the use of the warm tub, the attendant not only can wait for the pulsations to cease but he can strip the cord toward the child and thus add still further to its blood volume. In addition to permitting time for this autotransfusion, the warm bath also makes it possible to aspirate retained material from the nasopharynx without chilling the child.

RESUSCITATION

All attempts to stimulate respiration should be made with great gentleness and under no circumstances should the child be plunged alternately into cold and hot water. Because the vital centers in the brain may be suffering from the results of anoxia produced during the delivery, the various chemical respiratory stimulants may do more harm than good. Carbon dioxide and alphalobelin, accordingly, should not be used until the attendant is certain that sufficient oxygen is available to the brain cells to support their metabolic activity. If in doubt as to what to use, no harm and much good may result from the giving of oxygen.

BREECH

If breech extraction and internal version are accompanied by considerable fetal risk when these operations are done at full term, the risk should be and is much greater when the fetus is premature and fragile. Breech extraction and internal

version, therefore, are the most dangerous of all obstetrical operations when the child is premature and should not be done if they can be avoided. In breech presentation, external version before or at the onset of labor often can be accomplished, and the need for breech extraction at times may thus be eliminated.

CESAREAN SECTION

Cesarean section should be the safest method of delivering a premature infant. Most reports of premature end-results, on the contrary, show mortality figures much higher than might be expected. Of the 286 premature infants delivered alive by cesarean section in New York, 80, or 28 per cent, died within one month. These figures certainly do not favor suprapubic delivery. Even when considered from the standpoint of the various weight groups, the results are disappointing, as 13 per cent of the infants between 2,000 and 2,500 Gm. and 40 per cent of those between 1,500 and 2,000 Gm. failed to survive the first month (Table IV).

TABLE IV. PREMATURE MORTALITY, NEW YORK CITY, 286 CESAREAN SECTIONS

WT. IN GM.	NUMBER	DEATHS	MORTALITY %	MORTALITY FOR ALL PREMATURES %
Under 1,000	13	11	87	93
1,000-1,500	25	19	83	64
1,500-2,000	65	26	40	24
2,000-2,500	183	24	13	6
Total	286	80	28	18

When consideration is given to the fact that many of the sections were done for the worst cases of placenta previa and premature separation of the placenta, as well as in cardiac patients who had congestive failure, it may be stated that this method of delivery often was selected because of some grave maternal complication and that the fetal mortality frequently was due to the effect of that maternal complication rather than to the operation itself. We, accordingly, might take refuge behind this seemingly good explanation for our poor cesarean section results. On the other hand, might it not be well for us to review our own experience with a view to finding some constructive criticism which might better these results? In the light of my experience, the following suggestions seem warranted:

1. Cesarean section should be done only after consultation and roentgenologic examination indicate that the child is over 1,500 Gm. in weight, unless the life of the mother might be jeopardized by postponing the interruption of pregnancy.

2. Even after the fetus has reached the 1,500 Gm. limit, it is well to postpone operation if the condition of the mother and child will permit further delay.

3. Several hours before operation, vitamin K should be given to the mother as an aid in the prevention of hemorrhage.

4. No sedative drug should be given to the mother prior to operation.

5. The operation should be done under local anesthesia.

6. The low technique is preferable from the standpoint of both mother and child.

7. The child should not be grasped by the feet and violently jerked out of the uterus. On the contrary, it should be delivered head first by as gentle manipulations as circumstances will permit.

8. If there is no bleeding from the placental site and usually there is none when the low technique is followed, the cord should not be severed immediately. While waiting for its circulation to take up some of the placental blood, the child may be held by the feet so that whatever material is in the nasopharynx may drain away.

9. Vigorous methods of resuscitation should be avoided. When in doubt concerning the use of drugs, give oxygen rather than carbon dioxide and respiratory stimulants.

10. A tub of warm water or a warm crib should be at hand to prevent any unnecessary loss of heat while the infant is being transferred to its permanent quarters in the nursery.

SUMMARY

1. Although only 7.3 per cent of the total living infants of known weight born in New York City in 1939 were prematurely born, the prematures who died within thirty days made up almost 60 per cent of the total deaths under one month.

2. Of the 1,341 deaths under one month, 851, or 63 per cent, occurred on the first day.

3. The best way to prevent mortality in the groups weighing under 1,500 Gm. is to prevent conception of such infants or to delay their birth until they are large enough to withstand the hardships of extrauterine life.

4. Many premature deliveries may be prevented and the interruption of pregnancy postponed by adequate prenatal care.

5. If pregnancy is interrupted by cesarean section because of a fulminating toxemia, the operation should be done under local anesthesia and without the preliminary administration of sedatives.

6. In cardiac disease, congestive failure is especially dangerous to the premature infant. It, therefore, should be prevented by joint care of the mother by a competent cardiologist and obstetrician.

7. Syphilis should be recognized by the use of routine Wassermann determinations and prematurity prevented by vigorous treatment of the mother throughout pregnancy.

8. The dictum that there is no expectant treatment for placenta previa may have to be modified in the interests of the child. Careful observation in a good hospital and the use of large doses of progesterone might save some of the premature infants who are now lost in cases of placenta previa.

9. When a second twin lies longitudinally, it should be permitted to deliver spontaneously if possible. Only after a delay of at least one hour is version and extraction of a premature infant justifiable.

10. Before artificially interrupting pregnancy, the size of the child should be estimated by means of the x-ray and consultation with another competent obstetrician always is indicated.

11. In the management of premature labor, morphine, scopolamine, the barbiturates, and general anesthesia should not be given.

12. Vitamin K should be given to the mother before premature interruption of pregnancy is attempted and throughout all premature labors.

13. The membranes should be preserved as long as possible and episiotomy should be done to protect the premature infant from the pressure effects of labor.

14. If possible, premature infants should be placed in a tub of warm water immediately after birth and allowed to remain there until the cord stops pulsating.

15. Immediate tying of the cord robs the infant of the much needed blood which it otherwise might obtain from the placenta. Blood in the umbilical cord should be stripped toward the fetus before the umbilical cord is ligated.

16. Low forceps preceded by episiotomy is a desirable method of delivery, especially if the second stage tends to be prolonged.

17. Cesarean section at times is a valuable method of delivery. It should be done under local anesthesia without preliminary sedation. The child should be delivered head first, and, if possible, the tying of the cord should be somewhat delayed in order that the fetus may obtain some of the blood which is in the placental circulation.

I wish to thank Mr. Thomas J. Duffield and Dr. Sylvia L. Parker of the Bureau of Records for their kindness in furnishing me with the statistics on premature mortality in New York City.

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Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 11, 1941

The following papers were presented:

The Occipito-Posterior. Dr. D. Anthony D'Esopo (by invitation).

The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus. Dr. G. N. Papanicolaou (by invitation) and Dr. Herbert F. Traut. (For original article, see page 193.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MARCH 7, 1941

The following papers were presented:

Theca Cell Tumors of the Ovary. Drs. Samuel A. Wolfe and Irwin Neigus (by invitation). (For original article, see page 218.)

Remarks on Spinal Anesthesia in Obstetrics. Dr. Samuel Cosgrove, Jersey City, N. J. (by invitation).

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF MARCH 18, 1941

The following papers were presented:

Prophylactic External Cephalic Version. Dr. John L. Newell. (For original article, see page 256.)

Clinical Correlations of X-ray Pelvimetry by Thoms' Method. Dr. Robert H. Barker.

JOINT MEETING OF THE ST. LOUIS GYNECOLOGICAL SOCIETY, KANSAS CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY, AND CHICAGO GYNECOLOGICAL SOCIETY

FEBRUARY 15, 1941, AT ST. LOUIS, MO.

The following papers were presented:

A Study of the Ovaries and Endometriums of Patients With Fundal Carcinomas. Drs. Harold O. Jones and John I. Brewer. (For original article, see page 207.)

Chronic Cervicitis. Dr. George F. Pendleton, Kansas City, Mo.

ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF APRIL 10, 1941

The following papers were presented:

Pregnancy at Term Complicated by Old Poliomyelitis With Residual Paralysis and Scoliosis. (Motion Picture.) Dr. Paul Fletcher.

A Report of a Case of Amenorrhea and Sterility Treated With Progesterone. Dr. Willard M. Allen.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Gynecologic Operations

Baistrocchi, J. D.: The Transverse Incision in Gynecology, Semana méd. 47: 1079, 1940.

The author extols the virtues of transverse incision for performing gynecologic laparotomies. He describes and illustrates the incision he uses. This type of incision should be used in all pelvic laparotomies except for the removal of very large tumors and for the performance of Wertheim operations. This incision is a definite safeguard against postoperative hernias. If drainage is necessary, it can readily be accomplished through the transverse incision, and the subsequent results are better than after drainage in longitudinal incisions.

J. P. GREENHILL.

Long, W., and Poole, W. B.: Review of One Thousand Consecutive Hysterectomies, South. M. J. 33: 1015, 1940.

One thousand consecutive hysterectomies were performed by 49 attending surgeons in a general hospital during a four-and-one-half-year period with only 9 deaths and a mortality rate of 0.9 per cent. Four deaths occurred in 785 of the operations performed by 12 of the surgeons; there were but two fatalities (0.39 per cent) in 513 operations of this series done by 5 operators. Peritonitis accounted for 4 of the deaths; 3 resulted from pulmonary embolus, and 2 from operative shock.

The supravaginal procedures numbered 923, and accounted for 8 of the deaths. In 125 of these patients the cervix was either cauterized or amputated. Fifty-seven complete abdominal hysterectomies were performed without any mortality, and 20 vaginal operations with one death. Thus the cervix was either treated or removed in 202 patients. The cervical stump, although normal in appearance, should be examined periodically.

Operative risk is increased by the performance of multiple procedures. This factor may have been responsible for some of the complications and fatalities.

Total complications numbered 122, of which there were 47 urinary tract infections. There were 25 wound infections, an incidence of 2.5 per cent. In the last 500 cases, approximately 50 per cent of the patients had a temperature elevation for more than four days. Forty patients received transfusions preoperatively, and 8 after operation.

Hysterectomy is preferable to radium therapy in women under 41 years of age, since ovarian function may be preserved.

ARNOLD GOLDBERGER.

Cooke, W. R.: The Management of Salpingitis, South. Surgeon 8: 488, 1939.

The intelligent management of salpingitis is based upon a knowledge of regional anatomy, the pathology and sequelas of such infection, the defense mechanisms of the pelvic peritoneum and internal genitalia, and the type of bacteria involved. The principles upon which are based the management of suppurative infection in the general peritoneal cavity cannot be applied to the treatment of infections in the adnexa, and pelvic peritoneum. Gonococcal infection of the tube stimulates a defense mechanism which is effectively bacteriostatic and favors complete local recovery

without loss of function, providing that there is immediate and absolute bed rest. Local therapy and physical activity interfere with this reaction. The active phase of tubal inflammation subsides within seventy-two hours if bed rest is enforced at the earliest indication of salpingitis. Little damage is caused by unmixed gonococcal infection, and there is usually anatomic and functional recovery. Re-infections are usually accompanied by other organisms, and since these are in most instances of low virulence, the inherent defense mechanism continues to function, and the clinical course remains the same. Dominance of the secondary infecting bacteria is indicated by progressively active inflammation.

Gonococci tend to retain their virulence in the cervix for long periods and thus favor opportunities for autoinfection.

Diathermy, foreign protein therapy and Elliott treatment have not been of very great value in the treatment of acute gonorrheal salpingitis. Sulfanilamide may eradicate the source of re-infection in both the man and the woman; little effect can be expected upon most of the mixed infections. Operative treatment is never indicated in the active phase of infection, for at this time it is associated with a high postoperative mortality. The knowledge that regression of the infection may be followed by functional and anatomic restitution to normal with even the possibility of pregnancy should encourage the observance of a conservative regime.

Laparotomy is not performed until there has been an absence of temperature elevation above 99° F. for seventy-two hours following absolute confinement to bed, and unless the temperature does not rise following a vigorous pelvic examination at the end of this period. If the temperature fails to subside after the seventy-two-hour period of complete rest a daily examination should be made for collections of pus. These should be drained if detected.

ARNOLD GOLDBERGER.

Gardner, George H.: The Management of Chronic Pelvic Infections, Surg., Gynec. & Obst. **70**: 370, 1940.

Although pelvic infections still occupy an extremely important position among gynecologic problems, tubal disease is a less frequent indication for surgery nowadays.

Acute salpingitis should not be a surgical problem because the disease is usually self-limited. The period of morbidity is shorter with conservative management; furthermore, acutely inflamed structures are more likely to rehabilitate themselves if they are not mutilated by operative trauma.

If one is conservative, he will find that many pelvic masses resolve promptly and spontaneously without resorting to cul-de-sac drainage.

If the tubal involvement is a simple catarrhal inflammation and the fimbriae are free, one should not remove the tubes. If the tubes are thickened, filled with pus, and the fimbriae are sealed, they may be removed.

In pelvic surgery, drains through the posterior vaginal fornix are preferable to drains through the abdominal wall. The routine use of drains after a total hysterectomy probably increases postoperative morbidity.

Sulfanilamide has found one of its chief fields of usefulness in the treatment of acute gonorrhea and in the management of postabortive and puerperal infections. Enthusiasm has been shown about pelvic heat therapy as an aid in hastening resolution of subacutely inflamed pelvic structures.

Relatively few women with acute gonorrheal salpingitis, postabortive infections, and puerperal sepsis ultimately require surgery for the correction of the residues of the acute inflammation.

One should wait at least a year, or preferably a year and one-half, after an acute attack of gonorrheal salpingitis has subsided before operating, the only exception being the individual who repeatedly is reinfected. Under such circumstances the operation should be performed soon after an acute attack has subsided, before she has an opportunity to become infected again. After a cellulitis type of infection one should postpone operation indefinitely. The presence of fever is a contraindication to surgical interference, unless one is operating to drain an abscess or to remove it. Exquisite pelvic tenderness, induration of tissues, and the presence of cellulitis usually denote a relatively active infection.

Genital tuberculosis is rare. Radical operative procedures are indicated; usually, it is unwise to preserve an ovary in the face of a tuberculous infection.

Today, most gynecologists recognize the relationship of violin-string adhesions over the liver to genital gonorrhea.

If one removes both Fallopian tubes, the corpus of the uterus also should be removed. If one ovary is diseased and the other one is normal, the diseased ovary should be removed in toto.

WILLIAM C. HENSKE.

Chalier, Andre: The Condition of the Adnexa in Uterine Fibroids and Their Surgical Sequelae, Presse méd. **47**: 1221, 1939.

In the effort to determine the frequency and nature of associated adnexal disease, the author reviewed 600 cases which had been treated for uterine fibroids. He found 212 records containing a complete description of the adnexa.

In the therapeutic management of uterine fibroids, two main principles must constantly be borne in mind: first, the attendant risk of the selected procedure, and second, the possibility of maintaining physiologic function in the postoperative period.

In the 212 analyzed cases, the adnexa were recorded as normal in only 51 instances; while in approximately 75 per cent, they were in a pathologic condition. He divides the associated adnexal diseases into 3 groups: processes involving one or both ovaries, affecting one or both Fallopian tubes, and last, those involving both the tubes and ovaries.

The adnexal disease was limited to one or both ovaries in 104 cases (circa 50 per cent). This included atrophy of the ovary in 14 cases, larger ovarian lesions, seldom over orange size, in 17 and microcystic or poly- or sclerocystic ovaries in 73 cases, these latter being bilateral 46 times (21.69 per cent).

Tubal disease, in 11 cases included bilateral pyosalpinx (3), bilateral hydrohematosalpinx (5), bilateral hydrosalpinx (2), and bilateral tuberculous salpingitis (1).

Mixed tuboovarian conditions, present in 45 cases (21.2 per cent) included periadenitis of prolapsed adnexa (3 cases) and true adnexitis (32 cases).

In these 161 instances of associated adnexal pathology, there were 69 cases of serious tubal, ovarian, or tuboovarian disease while in the other 73 cases the pathologic changes were of minor importance.

The 212 requiring uterine operations included 150 supravaginal hysterectomies and 38 total hysterectomies. In 24 cases more conservative surgery could be done: 6 subisthmial hysterectomies, 3 defundations, and 15 myomectomies.

Salvage of ovarian tissue during the concomitant adnexal surgery was possible in 98 instances, in 74 cases by conservation of ovarian tissue *in situ*, and in the remaining 24 operations by complete or partial ovarian grafts into the labia majora.

The author in conclusion stresses the advantage of conservatism by leaving some ovarian tissue in situ. He does not favor ovarian grafts. He had but one case in which preserved adnexa required operative reintervention, an ovarian infarction following removal of a uterine fibroid.

CLAIR E. FOLSOME.

Wharton, Lawrence R.: Further Experiences in the Construction of the Vagina, Ann. Surg. **111**: 1010, 1940.

The author reports on 12 cases of constructing a vagina according to his suggested technique. The operation consists chiefly in the blunt dissection of the rectovesical space. Into this space is fitted a form of light but fairly rigid material which will not adhere to the raw vaginal walls. The author used a mold of Balsa wood covered with a rubber condom. The operation was performed by 7 different operators. The results were perfect in 8 cases, unknown in 1 case, and complete or partial failure in 3 cases. Sexual life was normal and orgasm was definitely experienced by some of the women. The vaginal mold should be sufficiently rigid to resist the constant pressure of the perineal muscles, it should be smooth, clean, sterilizable, nonabsorbent, and light so that it will not press against the rectum. The

additional use of mucous membrane grafts is not of much value, although a few pinch grafts over the end of the vaginal form have been used. Bleeding was the chief complication of this operation.

Postoperative care is important and consists chiefly of keeping the vesicorectal space clean. It may be irrigated with salt solution or boric acid. A weak antiseptic solution, such as 2 per cent mercurochrome, may be used to paint the walls of this space. The lubricated form must be worn most of the time for two months. Intercourse is prohibited until the epithelium is thick and strong. The author lists two chief causes for failure. The first is due to failure to wear the vaginal form and the second to injury to the bladder or rectum that sometimes occurs in the course of the dissection.

WILLIAM BERMAN.

Grossmann, Hans: The Production of an Artificial Vagina by the Formation of Broad Based Skin Flaps, Zentralbl. f. Gynäk. **63**: 1810, 1939.

Some of the various operations for the formation of artificial vagina are listed. The author objects to the fact that most are unduly complicated. He describes a simple method which has been satisfactory in his hands in three cases. Broad based flaps of skin are made on each side and posteriorly. The former include the labia minora and majora which are adjacent. The usual dissection is followed by the apposition of these flaps and the usual postoperative care. This skin is said to be sufficiently loose and mobile to produce long flaps. The case described in detail ended up with a vagina 10 cm. long which admitted two fingers.

The ultimate character of the vagina and the fate of accessory skin structures is not described. Indications are not discussed. Three illustrations describe the formation of the flaps and the results.

J. L. MCKELVEY.

Matassarin: Rose Operation Repair of the Trigonal Muscle (Incontinence in the Female), J. Kansas Med. Soc. **61**: 189, 1940.

In 90 per cent of these women a repair of the cystocele and perineum will give the desired relief but the other 10 per cent are not relieved of their dribbling, and many, though relieved of the incontinence, still have a marked dysuria.

This operation is done in the following manner: Royston and Rose use twilight sleep and local anesthesia of ¼ per cent novocaine with 4 min. 1:1000 adrenalin per ounce, as they believe it facilitates the dissection of the tissues and gives better hemostasis. It may be done, also, under a general or spinal anesthetic.

The incision is an inverted T through the anterior vaginal wall from cervix to a point 1 cm. from external meatus. The vaginal flap is dissected from the bladder, being very careful to avoid injury to the urethra. The bladder is then freed from uterus by blunt dissection. The base of the incision is now carried far enough laterally to expose the base of the broad ligaments. A No. 18 French, pezzar catheter is inserted into the bladder. Traction on the catheter will clearly mark the site of the internal sphincter, just in front of the bulbous tip. Using 00 or 000 chromic catgut on a fine curved intestinal needle take a deep bite anteroposteriorly in the tissues close to the urethra approximately three-fourths of an inch behind the internal sphincter. Emphasis is placed on carrying the suture anteriorly to within 1 cm. of the meatus. Care must be taken not to carry this suture too far posteriorly, to obstruct the ureteral orifice which is normally 3 cm. behind the internal sphincter. This suture is not tied at present. Now, a similar suture is placed on the opposite side. If the cystocele is marked, a third similar suture should be placed in midline. These sutures will restore the normal axis of the urethra.

A deep mattress suture of the same material (Kelly stitch) is then placed to reinforce the internal sphincter and fix it around the trigonal muscle. The pezzar catheter is removed before any of these sutures are tied.

With No. 1 chromic catgut the fascia is brought together and reinforced with another row of sutures. The bases of the broad ligaments are sutured anteriorly to the cervix, thus elevating it. The redundant vaginal mucosa is trimmed away and the incision sutured with No. 1 chromic catgut. A perineal repair is usually added.

Unless the cystocele is very marked, there is no reason for the use of a retention catheter, however, if one is used it should be of plain soft rubber and must be introduced carefully and removed after five to seven days with exceeding care. In exceptional cases with little cystocele when no perineorrhaphy is done the patient may be up in a chair after two or three days and up and about in a few days more.

J. P. GREENHILL.

Pilcher, Frederick Jr., and Aikenhead, A. E.: Accidental Bilateral Ligation of the Ureters, Canad. M. A. J. **43**: 436, 1940.

The authors report a case of accidental bilateral ligation of the ureters during the course of a total hysterectomy. Treatment consisted of bilateral nephrostomy. Four weeks later one ureter had become patent to a ureteral catheter and shortly thereafter the nephrostomy tube on the opposite side dropped out. Intravenous pyelography ten months postoperatively demonstrated normal kidney pelves, calyces, and ureters.

From a review of the literature the authors believe that the best treatment for such accidents is immediate nephrostomy rather than attempts at deligation. This should be followed later by appropriate treatment for the obstructing lesion such as end-to-end anastomosis or implantation of the ureter into the bladder or rectum. In many instances of simple ligation the lumen may be restored spontaneously.

CARL P. HUBER.

Knott, W.: The Prevention of Postoperative Thrombosis and Embolism by Means of Elevation of the Lower Extremities, Zentralbl. f. Gynäk. **62**: 679, 1939.

Two series of obstetric-gynecologic operative cases (630 and 670 cases, respectively) were treated by similar methods for the prevention of thrombosis and embolism except that the latter group were kept for ten days with the lower extremities elevated. All patients were given a drug, "Sympatol," for a few days before operation and for fourteen days thereafter. Patients over fifty years of age and those upon whom plastic operations had been done were out of bed for short periods daily, beginning with the day of operation or the next day. Leeches were applied to the thighs on the day following operation. Except for the elevation of the foot of the bed, all patients were similarly treated. With this procedure deaths from embolism fell from 6 to 4, embolism from 20 to 5 and phlebitis from 4 to 1. Thrombosis increased from 10 to 13 cases. Details of the cases are given. The author suggests that the results warrant further investigation.

J. L. MCKELVEY.

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 3, 1942, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I examinations must be on file in the Secretary's Office not later than October 6, 1941. Applications for Group A must be in the Secretary's Office by March 1, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., immediately prior to the 1942 meeting of the American Medical Association.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Graduate Training in Obstetrics and Gynecology

The following is an excerpt from the report of the Committee on Graduate Study of the American Board of Obstetrics and Gynecology, presented at its recent meeting, May 27, 1941, at Cleveland, Ohio:

The Graduate Committee of the Board has kept in contact during the year with the Council on Medical Education and Hospitals of the A. M. A. The Council has sent the Committee a number of application blanks from hospitals requesting the approval of the A. M. A. and of the American Board on residencies in obstetrics and gynecology. The blanks which are used in these reports were arranged last year by the A. M. A. and the Graduate Committee and were presented to the Board at its annual meeting in Atlantic City.

It was decided that the recommendations of the Committee to the A. M. A. would be on the following basis: full approval, which is unqualified approval; provisional approval, which would require review of the situation within a year; action deferred, in which, in the opinion of the Committee, the conditions for approval or provisional approval have not been met, but which may be considered again within a year or two; nonapproval.

Hospitals requesting approval of residencies are allocated according to the recommendations of the Committee.

In addition the Council on Medical Education and Hospitals sent to the Committee for consideration similar blanks filled out by hospitals which had been approved previously by the Council on Medical Education and Hospitals and our Committee's action on these hospitals is enclosed.

A brief draft of the minimum requirements for residencies in obstetrics and/or obstetrics and gynecology was drawn up. In so far as possible such suggestions as have been agreed upon by the Committee have been incorporated in this draft which is herewith submitted for the discussion of the Board.

MINIMUM REQUIREMENTS FOR RESIDENCIES IN OBSTETRICS AND/OR GYNECOLOGY

In addition to the items on the combined report blank of the Council on Medical Education and Hospitals of the A. M. A. and the American Board of Obstetrics and Gynecology, the candidate should have the following training or its equivalent:

At least one year of hospital internship, preferably rotating, which should include service in a well-organized department of obstetrics and/or gynecology.

Following this the candidate should have the equivalent of three years' training in obstetrics and/or gynecology, preferably both, under the supervision of competent obstetricians and gynecologists, some of whom, at least, should hold the certificates of the American Board.

During the three years he should have clinical work in obstetrics and/or gynecology to include prepartum clinics and gynecologic diagnosis; out-patient obstetrics, ambulatory gynecology and minor gynecologic operations are desirable; obstetric hospital service consisting of assisting in and delivery of normal and complicated labors; gynecologic hospital service which should consist of both nonoperative and operative services.

To be approved for residency a hospital should have at least 350 obstetric deliveries and an equal number of cases of gynecologic cases yearly; in such a limited service there should be at least 100 "free" deliveries. Three or more years of graduate training need not necessarily be spent in one hospital or institution.

The candidate should have an adequate working knowledge of gross and microscopic obstetric and gynecologic pathology. If the three years are spent in one hospital or institution, organized instruction in pathology or other basic sciences should be provided. If the graduate obtains his complete training in several hospitals it would be extremely difficult for him to obtain sufficient instruction in pathology unless the various hospitals offering residencies of a year or more should arrange for such instruction. It is desirable for the trainee to have three months' full-time service in pathology or a specified number of hours weekly combined with another service for an equivalent period of time.

Candidates for the certificate of the American Board of Obstetrics and Gynecology may be eligible for examination by the Board whose graduate training was obtained under the preceptorship of a competent obstetrician and gynecologist and not necessarily as a resident or fellow in a hospital or graduate institution.

The lists of hospitals approved for graduate training in obstetrics and gynecology are published from time to time in the Educational Number of *The Journal of the American Medical Association.*

Books Received

THE THERAPEUTICS OF INTERNAL DISEASES. Volume III. Supervising Editor George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., and Associate Editor Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. 1941, New York, D. Appleton-Century Company, Inc.

DIE GYNAEKOLOGISCHEN OPERATIONEN. Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. Zweite verbesserte Auflage, 424 Seiten, mit 427, zum groessten Teil farbigen Abbildungen und Bilderreihen von Kaethe Droysen. 1941, Leipzig, Verlag von Georg Thieme.

FEMALE SEX HORMONES. By Edward A. Doisy, Philip E. Smith, Robert T. Frank, and Elmer L. Sevringhaus. 58 pages. 1941, Philadelphia, University of Pennsylvania Press.

SPERMATOZOA AND STERILITY. By Abner I. Weisman, M.D., Adjunct Gynecologist, Jewish Memorial Hospital, N. Y., etc. With a Foreword by Robert L. Dickinson. 314 pages, 77 illustrations. 1941, New York, Paul B. Hoeber, Inc.

YOU CAN BE HAPPILY MARRIED. By Gilbert Applehof, Jr., Rector of St. John's Church, Alma, Mich. 218 pages. 1941, New York, The Macmillan Company.

THE DOCTOR TAKES A HOLIDAY. By Mary McKibbin-Harper, M.D. Illustrated, 349 pages. The Torch Press, Cedar Rapids, Iowa, 1941.

HANDBOOK OF ANAESTHETICS. Revised by R. J. Minnitt, M.D., Lecturer in Anaesthesia, University of Liverpool, etc. With chapters on local and spinal anaesthesia by W. Quarry Wood, M.D., Surgeon, Edinburgh Royal Infirmary. Fifth edition, 103 illustrations, 364 pages. 1940, Baltimore, Williams and Wilkins Company.

MALIGNANT DISEASE AND ITS TREATMENT BY RADIUM. By Stanford Cade, F.R.C.S., Surgeon, Westminster Hospital, etc. 1280 pages, 623 illustrations, many in color. 1940, Baltimore, Williams and Wilkins Company.